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(54) Title: INTERFERON-ALPHA INDUCED GENES

(57) Abstract: The present disclosure relates to identification of previously known genes as being genes upregulated by interferon-α administration, in particular the human genes corresponding to the cDNA sequence in GenBank designated g4758303, g5453897, g4505186, g2366751, g33917, g4504962, g3978516, g5924396, g4505656, g1504007, g3702446, g4001802, g292289, g4557226, g4507646 and g4507170. Determination of expression products of these genes is proposed as having utility in predicting responsiveness to treatment with interferon-α and other interferons which act at the Type 1 interferon receptor.

INTERFERON-ALPHA INDUCED GENES

Field of the Invention

The present invention relates to identification of previously known genes as genes upregulated by interferon-α (IFN-α) administration. Detection of expression products of these genes is thus now proposed as a means for predicting responsiveness to IFN-α and other interferons which act at the Type 1 interferon receptor.

Background of the Invention

IFN-α is widely used for the treatment of a number of disorders. Disorders which may be treated using IFN-α include neoplastic diseases such as leukemia, lymphomas, and solid tumours, AIDS-related Kaposi's sarcoma and viral infections such as chronic hepatitis. IFN-α has also been proposed for administration via the oromucosal route for the treatment of autoimmune, mycobacterial, neurodegenerative, parasitic and viral disease. In particular, IFN-α has been proposed, for example, for the treatment of multiple sclerosis, leprosy, tuberculosis, encephalitis, malaria, cervical cancer, genital herpes, hepatitis B and C, HIV, HPV and HSV-1 and 2. It has also been suggested for the treatment of arthritis, lupus and diabetes. Neoplastic diseases such as multiple myeloma, hairy cell leukemia, chronic myelogenous leukemia, low grade lymphoma, cutaneous T-cell lymphoma, carcinoid tumours, cervical cancer, sarcomas including Kaposi's sarcoma, kidney tumours, carcinomas including renal cell carcinoma, hepatic cellular carcinoma, nasopharyngeal carcinoma, haematological malignancies, colorectal cancer, glioblastoma, laryngeal papillomas, lung cancer, colon cancer, malignant melanoma and brain tumours are also suggested as being treatable by administration of IFN-α via the oromucosal route, i.e. the oral route or the nasal route.

IFN-α is a member of the Type 1 interferon family, which exert their characteristic biological activities through interaction with the Type 1 interferon receptor. Other Type 1 interferons include IFN-β, IFN-ω and IFN-τ.

Unfortunately, not all potential patients for treatment with a Type 1 interferon such as interferon-α, particularly, for example, patients suffering from chronic viral hepatitis, neoplastic disease and relapsing remitting multiple sclerosis, respond favourably to Type 1 interferon therapy and only a fraction of those who do respond exhibit long-term benefit. The inability of the physician to confidently predict the therapeutic outcome of Type 1 interferon treatment raises serious concerns as to the cost-benefit ratio of such treatment, not only in terms of wastage of an expensive biopharmaceutical and lost time in therapy, but also in terms of the serious side effects to which the patient is exposed. Furthermore, abnormal production of IFN-α has been shown to be associated with a number of autoimmune diseases. For these reasons, there is much interest in identifying Type 1 interferon responsive genes since Type 1 interferons exert their therapeutic action by modulating the expression of a number of genes. Indeed, it is the specific pattern of gene expression induced by Type 1 interferon treatment that determines whether a patient will respond favourably or not to the treatment.

Summary of the Invention

It has now been found that the human genes corresponding to the cDNA sequences in GenBank assigned accession nos. g4758303, g5453897, g4505186, g2366751, g33917, g4504962, g3978516, g5924396, g4505656, g1504007, g3702446, g4001802, g292289, g4557226, g4507646 and g4507170 correspond to mouse genes upregulated by administration of IFN-α by an oromucosal route or intravenously.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no. g4758303 was previously noted in GenBank as encoding a protein disulphide isomerase-related protein (ERP-70) but was not previously recognised as

being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g5453897 was previously noted in GenBank as encoding a protein termed peptidyl-prolyl cis/trans isomerase NIMA-interacting 1 (PIN-1) but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g4505186 was previously noted in GenBank as encoding a monokine induced by gamma interferon (MIG) but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g2366751 was previously noted in GenBank as encoding a lysyl tRNA synthetase (LTS) but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g33917 was previously noted in GenBank as encoding a gamma-interferon inducible early response gene (IP-10) with homology to platelet proteins but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g4504962 was previously noted in GenBank as encoding Lipocalin 1 but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g3978516 was previously noted in GenBank as encoding SEC 63 but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g5924396 was previously noted in GenBank as encoding surfeit 6 but

was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g4505656 was previously noted in GenBank as encoding a cGMP-stimulated phosphodiesterase 2A (PDE2A) but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g1504007 was previously noted in GenBank as encoding KIAA0212 but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g3702446 was previously noted in GenBank as encoding a phosphatidylinositol 4-kinase (NPIK-B) but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g4001802 was previously noted in GenBank as encoding BAF53a but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g292289 was previously noted in GenBank as encoding a MADS/MEF2-family transcription factor (MEF2C) but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g4557226 was previously noted in GenBank as encoding an arylacetamide deacetylase (AADAC) but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g4507646 was previously noted in GenBank as encoding α

tropomyosin 1 (TPM1) but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

The human gene corresponding to the cDNA sequence in GenBank assigned accession no g4507170 was previously noted in GenBank as encoding secreted protein that is acidic and rich in cysteine (SPARC) but was not previously recognised as being of interest in relation to Type 1 interferon administration. It is now also designated an IFN-α upregulated gene.

Determination of the level of one or more of ERP-70, PIN-1, MIG, LTS, IP-10, Lipocalin 1, SEC 63, surfeit 6, PDE2A, KIAA0212, NPIK-B, BAF53a, MEF2C, AADAC, TPM1 or SPARC protein or a naturally-occurring variant thereof, or the corresponding mRNA, in cell samples of Type 1 interferon-treated patients, e.g. patients treated with IFN-α, e.g. such as by the oromucosal route or intravenously, may thus be used to predict responsiveness to such treatment. It has additionally been found that alternatively and more preferably, such responsiveness may be judged, for example, by treating a sample of human peripheral blood mononuclear cells *in vitro* with a Type 1 interferon and looking for upregulation or downregulation of expression products, preferably mRNA, corresponding to the same gene or genes.

Brief description of the sequences

SEQ. ID. No.1 is the sequence of the cDNA designated in Genbank as accession no.g4758303 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.2 is the amino acid sequence alone of ERP-70 corresponding to GenBank accession no. g4758304.

SEQ. ID. No.3 is the sequence of the cDNA designated in Genbank as accession no.g5453897 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.4 is the amino acid sequence alone of PIN-1 corresponding to GenBank accession no. g5453898.

SEQ. ID. No.5 is the sequence of the cDNA designated in Genbank as accession no.g4505186 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.6 is the amino acid sequence alone of MIG corresponding to GenBank accession no. g4505187.

SEQ. ID. No.7 is the sequence of the cDNA designated in Genbank as accession no.g2366751 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.8 is the amino acid sequence alone of LTS corresponding to GenBank accession no. g2366752.

SEQ. ID. No.9 is the sequence of the cDNA designated in Genbank as accession no.g33917 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.10 is the amino acid sequence alone of IP-10 corresponding to GenBank accession no. g33918.

SEQ. ID. No.11 is the sequence of the cDNA designated in Genbank as accession no.g4504962 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.12 is the amino acid sequence alone of Lipocalin 1 corresponding to GenBank accession no. g4504963.

SEQ. ID. No.13 is the sequence of the cDNA designated in Genbank as accession no.g3978516 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.14 is the amino acid sequence alone of SEC 63 corresponding to GenBank accession no. g3978517.

SEQ. ID. No.15 is the sequence of the cDNA designated in Genbank as accession no.g5924396 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.16 is the amino acid sequence alone of surfeit 6 corresponding to GenBank accession no. g5924396.

SEQ. ID. No.17 is the sequence of the cDNA designated in Genbank as accession no.g4505656 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.18 is the amino acid sequence alone of PDE2A corresponding to GenBank accession no. g4505656.

SEQ. ID. No.19 is the sequence of the cDNA designated in Genbank as accession no.g1504007 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.20 is the amino acid sequence alone of KIAA0212 corresponding to GenBank accession no. g1504008.

SEQ. ID. No.21 is the sequence of the cDNA designated in Genbank as accession no.g3702446 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.22 is the amino acid sequence alone of NPIK-B corresponding to GenBank accession no. g3702447.

SEQ. ID. No.23 is the sequence of the cDNA designated in Genbank as accession no.g4001802 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.24 is the amino acid sequence alone of BAF53a corresponding to GenBank accession no. g4001803.

SEQ. ID. No.25 is the sequence of the cDNA designated in Genbank as accession no.g292289 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.26 is the amino acid sequence alone of MEF2C corresponding to GenBank accession no. g292290.

SEQ. ID. No.27 is the sequence of the cDNA designated in Genbank as accession no.g4557226 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.28 is the amino acid sequence alone of AADAC corresponding to GenBank accession no. g4557226.

SEQ. ID. No.29 is the sequence of the cDNA designated in Genbank as accession no.g4507646 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.30 is the amino acid sequence alone of TPM1 corresponding to GenBank accession no. g4507647.

SEQ. ID. No.31 is the sequence of the cDNA designated in Genbank as accession no.g4507170 with the corresponding encoded polypeptide sequence shown below.

SEQ. ID. No.32 is the amino acid sequence alone of SPARC corresponding to GenBank accession no. g4507171.

Detailed description

The present invention provides a method of predicting responsiveness of a patient to treatment with a Type 1 interferon, e.g. IFN-α treatment (such as IFN-α treatment by the oromucosal route or a parenteral route, for example, intravenously, subcutaneously or intramuscularly), which comprises determining the level of one or more of proteins selected from the proteins defined by the sequences set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30 or SEQ ID NO:32 and naturally-occurring variants thereof, e.g. allelic variants, or one or more of the corresponding mRNAs, in a cell sample from said patient, wherein said sample is obtained from said patient following administration of a Type 1 interferon, or is treated prior to said determining with a Type 1 interferon such as IFN-α *in vitro*. Such determining may be combined with determination of any other protein or mRNA whose expression is known to be affected in human cells by Type 1 interferon administration e.g. IFN-α administration.

Preferably, the Type 1 interferon for testing responsiveness will be the Type 1 interferon selected for treatment. It may be administered by the proposed treatment route and at the proposed treatment dose. Preferably, the subsequent sample analysed

may be, for example, a blood sample or a sample of peripheral blood mononuclear cells (PBMCs) isolated from a blood sample.

More conveniently and preferably, a sample obtained from the patient comprising PBMCs isolated from blood may be treated *in vitro* with a Type 1 interferon, e.g. at a dosage range of about 1 to 10,000 IU/ml. Such treatment may be for a period of hours, e.g. about 7 to 8 hours. Preferred treatment conditions for such *in vitro* testing may be determined by testing PBMCs taken from normal donors with the same interferon and looking for upregulation of an appropriate expression product. Again, the Type 1 interferon employed will preferably be the Type 1 interferon proposed for treatment of the patient, e.g. recombinant IFN-α. PBMCs for such testing may be isolated in conventional manner from a blood sample using Ficoll-Hypaque density gradients. An example of a suitable protocol for such *in vitro* testing of Type 1 interferon responsiveness is provided in Example 18 below.

The sample, if appropriate after *in vitro* treatment with a Type 1 interferon, may be analysed for the level of one or more of ERP-70, PIN-1, MIG, LTS, IP-10, Lipocalin 1, SEC 63, surfeit 6, PDE2A, KIAA0212, NPIK-B, BAF53a, MEF2C, AADAC, TPM1 or SPARC protein or a naturally-occurring variant thereof. This may be done using an antibody or antibodies capable of specifically binding one or more of ERP-70, PIN-1, MIG, LTS, IP-10, Lipocalin 1, SEC 63, surfeit 6, PDE2A, KIAA0212, NPIK-B, BAF53a, MEF2C, AADAC, TPM1 or SPARC protein and naturally-occurring variants thereof, eg. allelic variants thereof. Preferably, however, the sample will be analysed for mRNA encoding ERP-70, PIN-1, MIG, LTS, IP-10, Lipocalin 1, SEC 63, surfeit 6, PDE2A, KIAA0212, NPIK-B, BAF53a, MEF2C, AADAC, TPM1 or SPARC protein or a naturally-occurring variant thereof. Such mRNA analysis may employ any of the techniques known for detection of mRNAs, e.g. Northern blot detection or mRNA differential display. A variety of known nucleic acid amplification protocols may be employed to amplify any mRNA of interest present in the sample, or a portion thereof, prior to detection. The mRNA of interest, or a corresponding amplified nucleic acid, may be probed for using a nucleic acid probe attached to a solid support. Such a solid support may be a micro-array

carrying probes to determine the level of further mRNAs or amplification products thereof corresponding to Type 1 interferon upregulated genes, e.g. such genes identified as upregulated in response to oromucosal or intravenous administration of IFN-α. Methods for constructing such micro-arrays (also referred to commonly as nucleic acid, probe or DNA chips) are well-known (see, for example, EP-B 0476014 and 0619321 of Affymax Technologies N.V. and Nature Genetics Supplement January 1999 entitled "The Chipping Forecast").

The following examples illustrate the invention:

Examples

Example 1

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10µg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display

Analysis (Lang, P. and Pardee, A.B., Science, 257, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g4758303. The corresponding polypeptide sequence is GenBank sequence g4758304, which is noted in GenBank as corresponding to ERP-70.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g4758303 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 1 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 2

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some

30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10μg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 μg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out,

reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

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Identification of Human cDNA

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One such cDNA was found to correspond to GenBank cDNA sequence g5453897. The corresponding polypeptide sequence is GenBank sequence g5453898, which is noted in GenBank as corresponding to PIN-1.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g5453897 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 3 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 3

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10µg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine

EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g4505186. The corresponding polypeptide sequence is GenBank sequence g4505187, which is noted in GenBank as corresponding to MIG.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g4505186 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 5 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 4

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10μg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 μg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g2366751. The corresponding polypeptide sequence is GenBank sequence g2366752, which is noted in GenBank as corresponding to LTS.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g2366751 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood

mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 7 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 5

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10µg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 µg was

reverse-transcribed in 100 µl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 µl of the reverse transcription sample in 10 µl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfi* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g33917. The corresponding polypeptide sequence is GenBank sequence g33918, which is noted in GenBank as corresponding to IP-10.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g33917 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 9 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 6

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in

phosphate buffered saline (PBS), 10μg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 μg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, 257, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g4504962. The corresponding polypeptide sequence is GenBank sequence g4504963, which is noted in GenBank as corresponding to Lipocalin 1.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g4504962 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 11 when human peripheral blood mononuclear cells are treated with IFN-α as described

in Example 18 below.

Example 7

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10µg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 µg was reverse-transcribed in 100 µl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA,

CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 µl of the reverse transcription sample in 10 µl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g3978516. The corresponding polypeptide sequence is GenBank sequence g3978517, which is noted in GenBank as corresponding to SEC 63.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g3978516 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 13 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 8

Previous experiments had shown that the application of 5 μl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10μg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 μg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by

cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer

(Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g5924396. The corresponding polypeptide sequence is GenBank sequence g5924397, which is noted in GenBank as corresponding to surfeit 6.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g5924396 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 15 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 9

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10µg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 µg was reverse-transcribed in 100 µl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 µl of the reverse transcription sample in 10 µl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP

(3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g4505656. The corresponding polypeptide sequence is GenBank sequence g4505657, which is noted in GenBank as corresponding to PDE2A.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar

result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g4505656 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 17 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 10

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10µg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display

Analysis (Lang, P. and Pardee, A.B., Science, 257, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g1504007. The corresponding polypeptide sequence is GenBank sequence g1504008, which is noted in GenBank as corresponding to KIAA0212.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g1504007 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 119 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 11

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some

30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10μg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 μg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out,

reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g3702446. The corresponding polypeptide sequence is GenBank sequence g3702448, which is noted in GenBank as corresponding to NPIK-B.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g3702446 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 21 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 12

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10µg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing *Taq* DNA polymerase and α- ^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine

EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g4001802. The corresponding polypeptide sequence is GenBank sequence g4001803, which is noted in GenBank as corresponding to BAF53a.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g4001802 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 23 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 13

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10μg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 μg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing *Taq* DNA polymerase and α- ^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g292289. The corresponding polypeptide sequence is GenBank sequence g292290, which is noted in GenBank as corresponding to MEF2C.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g292289 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood

mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 25 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 14

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10µg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 µg was

reverse-transcribed in 100 µl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 µl of the reverse transcription sample in 10 µl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g4557226. The corresponding polypeptide sequence is GenBank sequence g4557227, which is noted in GenBank as corresponding to AADAC.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g4557226 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 27 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 15

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in

phosphate buffered saline (PBS), 10μg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 μg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, **257**, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g4507646. The corresponding polypeptide sequence is GenBank sequence g4507647, which is noted in GenBank as corresponding to TPM1.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accesssion no. g4507646 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 29 when human peripheral blood mononuclear cells are treated with IFN-α as described

in Example 18 below.

Example 16

Previous experiments had shown that the application of 5 µl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10µg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 µg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at -80°C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) **162**, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A.B., Science, 257, 967-971).

Differential Display Analysis

Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 µg was reverse-transcribed in 100 µl of reaction buffer using either one or the other of the three one-base anchored oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA,

CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 µl of the reverse transcription sample in 10 µl of amplification mixture containing *Taq* DNA polymerase and α-^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT11) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridise Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

Cloning and Sequencing

Re-amplified bands from the differential display screen were cloned in the *Sfr* 1 site of the pPCR-Script SK(+) plasmid (Stratagene), and cDNA amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

Identification of Human cDNA

Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA.

One such cDNA was found to correspond to GenBank cDNA sequence g4507170. The corresponding polypeptide sequence is GenBank sequence g4507171, which is noted in GenBank as corresponding to SPARC.

Other mouse genes upregulated in lymphoid tissue in response to oromucosal administration of IFN-α as described above have also been found to be upregulated in the spleen of mice in response to intravenous administration of IFN-α. A similar result is anticipated in respect of the mouse gene corresponding to the human gene identified by Genbank cDNA accession no. g4507170 when intravenous administration of IFN-α is carried out as described in Example 17 below.

Furthermore, mRNAs corresponding to human gene analogues of mouse genes found to be upregulated in response to oromucosal and intravenous administration of IFN-α have been found to be enhanced in human peripheral blood mononuclear cells following treatment with IFN-α *in vitro*. The same result is anticipated for mRNA corresponding to the cDNA as set forth in SEQ. ID. No. 31 when human peripheral blood mononuclear cells are treated with IFN-α as described in Example 18 below.

Example 17

Intravenous administration of IFN-α

Male DBA/2 mice are injected intravenously with 100,000 IU of recombinant murine IFN-α purchased from Life Technologies Inc. in 200 µl of PBS or treated with an equal volume of PBS alone. Eight hours later the animals are sacrificed by cervical dislocation and the spleen was removed using conventional procedures. Total RNA was extracted by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) 162, 156-159) and 10.0 µg of total RNA per sample is subjected to Northern blotting in the presence of glyoxal and hybridised with a cDNA probe for the mRNA of interest as described by Dandoy-Dron et al. (J. Biol. Chem. (1998) 273, 7691-7697). The blots are first exposed to autoradiography and then quantified using a Phospholmager according to the manufacturer's instructions.

Example 18

Testing Type 1 interferon responsiveness *in vitro*

Human peripheral blood mononuclear cells (PBMC) from normal donors are isolated on Ficoll-Hypaque density gradients and treated *in vitro* with 10,000 IU of recombinant human IFN-α2 (intron A from Schering-Plough) in PBS or with an equal volume of PBS alone. Eight hours later the cells are centrifuged (800 x g for 10 minutes) and the cell pellet recovered. Total RNA is extracted from the cell pellet by the method of Chomczynski and Sacchi and 10.0 μg of total RNA per sample is subjected to Northern blotting as described in Example 17 above.

The same procedure can be used to predict Type 1 interferon responsiveness using PBMC taken from a patient proposed to be treated with a Type 1 interferon.

CLAIMS:

1. A method of predicting responsiveness of a patient to treatment with a Type 1 interferon, which comprises determining the level of one or more proteins selected from the proteins defined by the sequences set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30 or SEQ ID NO: 32 and naturally-occurring variants thereof, or one or more of the corresponding mRNAs, in a cell sample from said patient, wherein said sample is obtained from said patient following administration of a Type 1 interferon or is treated prior to said determining with a Type 1 interferon *in vitro*.

2. A method as claimed in claim 1 wherein the interferon administered prior to obtaining said sample or used to treat said sample *in vitro* is the interferon proposed for treatment of the patient.

3. A method as claimed in claim 1 or 2 wherein a sample comprising peripheral blood mononuclear cells isolated from a blood sample of the patient is treated with a Type 1 interferon *in vitro*.

4. A method as claimed in any one of claims 1 to 3 wherein said determining comprises determining the level of one or more mRNAs encoding a protein selected from the proteins defined by the sequences set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30 or SEQ ID NO: 32 and naturally-occurring variants of said proteins.

5. A method as claimed in claim 4 wherein said mRNA, or a portion thereof, is amplified prior to detection.

6. A method as claimed in claim 4 or claim 5 wherein said mRNA, or an amplification product thereof, is detected by using a nucleic acid probe attached to a solid support.

7. A method as claimed in any one of claims 1 to 3 wherein said determining comprises determining the level of one or more proteins selected from the proteins defined by the sequences set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30 or SEQ ID NO: 32 and naturally-occurring variants thereof.

SEQUENCE LISTING

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     70                  75                  80

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Glu Phe Tyr Ala Pro Trp Cys Gly His Cys Lys Gln Phe Ala Pro Glu
 85                  90                  95                 100

tat gaa aaa att gcc aac ata tta aag gat aaa gat cct ccc att cct   393
Tyr Glu Lys Ile Ala Asn Ile Leu Lys Asp Lys Asp Pro Pro Ile Pro
                105                 110                 115
```

```
gtt gcc aag atc gat gca acc tca gcg tct gtg ctg gcc agc agg ttt   441
Val Ala Lys Ile Asp Ala Thr Ser Ala Ser Val Leu Ala Ser Arg Phe
            120                 125                 130

gat gtg agt ggc tac ccc acc atc aag atc ctt aag aag ggg cag gct   489
Asp Val Ser Gly Tyr Pro Thr Ile Lys Ile Leu Lys Lys Gly Gln Ala
        135                 140                 145

gta gac tac gag ggc tcc aga acc cag gaa gaa att gtt gcc aag gtc   537
Val Asp Tyr Glu Gly Ser Arg Thr Gln Glu Glu Ile Val Ala Lys Val
    150                 155                 160

aga gaa gtc tcc cag ccc gac tgg acg cct cca cca gaa gtc acg ctt   585
Arg Glu Val Ser Gln Pro Asp Trp Thr Pro Pro Pro Glu Val Thr Leu
165                 170                 175                 180

gtg ttg acc aaa gag aac ttt gat gaa gtt gtg aat gat gca gat atc   633
Val Leu Thr Lys Glu Asn Phe Asp Glu Val Val Asn Asp Ala Asp Ile
                185                 190                 195

att ctg gtg gag ttt tat gcc cca tgg tgt gga cac tgc aag aaa ctt   681
Ile Leu Val Glu Phe Tyr Ala Pro Trp Cys Gly His Cys Lys Lys Leu
            200                 205                 210

gcc ccc gag tat gag aag gcc gcc aag gag ctc agc aag cgt tct cct   729
Ala Pro Glu Tyr Glu Lys Ala Ala Lys Glu Leu Ser Lys Arg Ser Pro
        215                 220                 225

cca att ccc ctg gca aag gtc gac gcc acc gca gaa aca gac ctg gcc   777
Pro Ile Pro Leu Ala Lys Val Asp Ala Thr Ala Glu Thr Asp Leu Ala
    230                 235                 240

aag agg ttt gat gtc tct ggc tat ccc acc ctg aaa att ttc cgc aaa   825
Lys Arg Phe Asp Val Ser Gly Tyr Pro Thr Leu Lys Ile Phe Arg Lys
245                 250                 255                 260

gga agg cct tat gac tac aac ggc cca cga gaa aaa tat gga atc gtt   873
Gly Arg Pro Tyr Asp Tyr Asn Gly Pro Arg Glu Lys Tyr Gly Ile Val
                265                 270                 275

gat tac atg atc gag cag tcc ggg cct ccc tcc aag gag att ctg acc   921
Asp Tyr Met Ile Glu Gln Ser Gly Pro Pro Ser Lys Glu Ile Leu Thr
            280                 285                 290

ctg aag cag gtc cag gag ttc ctg aag gat gga gac gat gtc atc atc   969
Leu Lys Gln Val Gln Glu Phe Leu Lys Asp Gly Asp Asp Val Ile Ile
        295                 300                 305

atc ggg gtc ttt aag ggg gag agt gac cca gcc tac cag caa tac cag   1017
Ile Gly Val Phe Lys Gly Glu Ser Asp Pro Ala Tyr Gln Gln Tyr Gln
    310                 315                 320
```

```
gat gcc gct aac aac ctg aga gaa gat tac aaa ttt cac cac act ttc   1065
Asp Ala Ala Asn Asn Leu Arg Glu Asp Tyr Lys Phe His His Thr Phe
325                 330                 335                 340

agc aca gaa ata gca aag ttc ttg aaa gtc tcc cag ggg cag ttg gtt   1113
Ser Thr Glu Ile Ala Lys Phe Leu Lys Val Ser Gln Gly Gln Leu Val
                345                 350                 355

gta atg cag cct gag aaa ttc cag tcc aag tat gag ccc cgg agc cac   1161
Val Met Gln Pro Glu Lys Phe Gln Ser Lys Tyr Glu Pro Arg Ser His
            360                 365                 370

atg atg gac gtc cag ggc tcc acc cag gac tcg gcc atc aag gac ttc   1209
Met Met Asp Val Gln Gly Ser Thr Gln Asp Ser Ala Ile Lys Asp Phe
        375                 380                 385

gtg ctg aag tac gcc ctg ccc ctg gtt ggc cac cgc aag gtg tca aac   1257
Val Leu Lys Tyr Ala Leu Pro Leu Val Gly His Arg Lys Val Ser Asn
    390                 395                 400

gat gct aag cgc tac acc agg cgc ccc ctg gtg gtc gtc tac tac agt   1305
Asp Ala Lys Arg Tyr Thr Arg Arg Pro Leu Val Val Val Tyr Tyr Ser
405                 410                 415                 420

gtg gac ttc agc ttt gat tac aga gct gca act cag ttt tgg cgg agc   1353
Val Asp Phe Ser Phe Asp Tyr Arg Ala Ala Thr Gln Phe Trp Arg Ser
                425                 430                 435

aaa gtc cta gag gtg gcc aag gac ttc cct gag tac acc ttt gcc att   1401
Lys Val Leu Glu Val Ala Lys Asp Phe Pro Glu Tyr Thr Phe Ala Ile
            440                 445                 450

gcg gac gaa gag gac tat gct ggg gag gtg aag gac ctg ggg ctc agc   1449
Ala Asp Glu Glu Asp Tyr Ala Gly Glu Val Lys Asp Leu Gly Leu Ser
        455                 460                 465

gag agt ggg gag gat gtc aat gcc gcc atc ctg gac gag agt ggg aag   1497
Glu Ser Gly Glu Asp Val Asn Ala Ala Ile Leu Asp Glu Ser Gly Lys
    470                 475                 480

aag ttc gcc atg gag cca gag gag ttt gac tct gac acc ctc cgc gag   1545
Lys Phe Ala Met Glu Pro Glu Glu Phe Asp Ser Asp Thr Leu Arg Glu
485                 490                 495                 500

ttt gtc act gct ttc aaa aaa gga aaa ctg aag cca gtc atc aaa tcc   1593
Phe Val Thr Ala Phe Lys Lys Gly Lys Leu Lys Pro Val Ile Lys Ser
                505                 510                 515

cag cca gtg ccc aag aac aac aag gga ccc gtc aag gtc gtg gtg gga   1641
Gln Pro Val Pro Lys Asn Asn Lys Gly Pro Val Lys Val Val Val Gly
            520                 525                 530

aag acc ttt gac tcc att gtg atg gac ccc aag aag gac gtc ctc atc   1689
Lys Thr Phe Asp Ser Ile Val Met Asp Pro Lys Lys Asp Val Leu Ile
        535                 540                 545
```

```
gag ttc tac gcg cca tgg tgc ggg cac tgc aag cag cta gag ccc gtg   1737
Glu Phe Tyr Ala Pro Trp Cys Gly His Cys Lys Gln Leu Glu Pro Val
    550                 555                 560

tac aac agc ctg gcc aag aag tac aag ggc caa aag ggc ctg gtc atc   1785
Tyr Asn Ser Leu Ala Lys Lys Tyr Lys Gly Gln Lys Gly Leu Val Ile
565                 570                 575                 580

gcc aag atg gac gcc act gcc aac gac gtc ccc agc gac cgc tat aag   1833
Ala Lys Met Asp Ala Thr Ala Asn Asp Val Pro Ser Asp Arg Tyr Lys
                585                 590                 595

gtg gag ggc ttc ccc acc atc tac ttc gcc ccc agt ggg gac aaa aag   1881
Val Glu Gly Phe Pro Thr Ile Tyr Phe Ala Pro Ser Gly Asp Lys Lys
            600                 605                 610

aac cca gtt aaa ttt gag ggt gga gac aga gat ctg gag cat ttg agc   1929
Asn Pro Val Lys Phe Glu Gly Gly Asp Arg Asp Leu Glu His Leu Ser
        615                 620                 625

aag ttt ata gaa gaa cat gcc aca aaa ctg agc agg acc aag gaa gag   1977
Lys Phe Ile Glu Glu His Ala Thr Lys Leu Ser Arg Thr Lys Glu Glu
    630                 635                 640

ctt tga aggcctgagg tctgcggaag gtgggaggag gcagacgccc tgcgtggccc    2033
Leu
645

atggtcgggg cgtccaccgg aggccggcaa caaacgacag tatctcggat tccttttttt 2093

ttttttttaa ttttttatac tttgttgttt cacttcatgc tctgaatact gaataaccat 2153

gaatgactga atagtttagt ccagattttt acagaggata catctatttt tatcattatt 2213

tggggtttga aaaatttttt tttacacctt ctaatttctt tatttctcaa agcagataat 2273

tcttctgtgt gaaaatgttt tctttttta atttaaggtt taaaattcct tttccaaatc 2333

atgttgattt tgctctttaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaagaagg 2393

gctgggacca accgggtgag atccacaagt ctctggatgt ggctgaaggc aaatacacaa 2453

ttgaagtact ttctgttttg aagtgctttc ccttttgaat ctggtttgaa acatgcagct 2513

tctgtctcta gcccaaggaa agaccaaaac atagggaaat aaaagcattt atctttgtct 2573

tggaagtaat tgttgaagtt gtgcagttga tcagtgcaca gttagctgca atgtttatag 2633

aaattgattg ttaaaccaaa tttacactgg catgtgtggt gtagtttcta aaaggcactt 2693

cacatttgaa atttttctta ccttagaaag tttctagtga tctaaatgtc tagttttgta 2753

ttcttttgtg tgtgttcact gtttctcagt attaccactt gaataattct ctgtacaggg 2813

gggtttgtgc tatacactgg gatgtctaat tgcagcaata aagcctttct t          2864
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<210> 2
<211> 646
<212> PRT
<213> Homo sapiens

<400> 2

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Met Arg Pro Arg Lys Ala Phe Leu Leu Leu Leu Leu Leu Gly Leu Val
  1               5                  10                  15

Gln Leu Leu Ala Val Ala Gly Ala Glu Gly Pro Asp Glu Asp Ser Ser
             20                  25                  30

Asn Arg Glu Asn Ala Ile Glu Asp Glu Glu Glu Glu Glu Glu Glu Asp
         35                  40                  45

Asp Asp Glu Glu Glu Asp Asp Leu Glu Val Lys Glu Glu Asn Gly Val
     50                  55                  60

Leu Val Leu Asn Asp Ala Asn Phe Asp Asn Phe Val Ala Asp Lys Asp
 65                  70                  75                  80

Thr Val Leu Leu Glu Phe Tyr Ala Pro Trp Cys Gly His Cys Lys Gln
                 85                  90                  95

Phe Ala Pro Glu Tyr Glu Lys Ile Ala Asn Ile Leu Lys Asp Lys Asp
            100                 105                 110

Pro Pro Ile Pro Val Ala Lys Ile Asp Ala Thr Ser Ala Ser Val Leu
        115                 120                 125

Ala Ser Arg Phe Asp Val Ser Gly Tyr Pro Thr Ile Lys Ile Leu Lys
    130                 135                 140

Lys Gly Gln Ala Val Asp Tyr Glu Gly Ser Arg Thr Gln Glu Glu Ile
145                 150                 155                 160

Val Ala Lys Val Arg Glu Val Ser Gln Pro Asp Trp Thr Pro Pro Pro
                165                 170                 175

Glu Val Thr Leu Val Leu Thr Lys Glu Asn Phe Asp Glu Val Val Asn
            180                 185                 190

Asp Ala Asp Ile Ile Leu Val Glu Phe Tyr Ala Pro Trp Cys Gly His
        195                 200                 205

Cys Lys Lys Leu Ala Pro Glu Tyr Glu Lys Ala Ala Lys Glu Leu Ser
    210                 215                 220

Lys Arg Ser Pro Pro Ile Pro Leu Ala Lys Val Asp Ala Thr Ala Glu
225                 230                 235                 240

Thr Asp Leu Ala Lys Arg Phe Asp Val Ser Gly Tyr Pro Thr Leu Lys
                245                 250                 255
```

```
Ile Phe Arg Lys Gly Arg Pro Tyr Asp Tyr Asn Gly Pro Arg Glu Lys
            260                 265                 270

Tyr Gly Ile Val Asp Tyr Met Ile Glu Gln Ser Gly Pro Pro Ser Lys
        275                 280                 285

Glu Ile Leu Thr Leu Lys Gln Val Gln Glu Phe Leu Lys Asp Gly Asp
    290                 295                 300

Asp Val Ile Ile Ile Gly Val Phe Lys Gly Glu Ser Asp Pro Ala Tyr
305                 310                 315                 320

Gln Gln Tyr Gln Asp Ala Ala Asn Asn Leu Arg Glu Asp Tyr Lys Phe
                325                 330                 335

His His Thr Phe Ser Thr Glu Ile Ala Lys Phe Leu Lys Val Ser Gln
            340                 345                 350

Gly Gln Leu Val Val Met Gln Pro Glu Lys Phe Gln Ser Lys Tyr Glu
        355                 360                 365

Pro Arg Ser His Met Met Asp Val Gln Gly Ser Thr Gln Asp Ser Ala
    370                 375                 380

Ile Lys Asp Phe Val Leu Lys Tyr Ala Leu Pro Leu Val Gly His Arg
385                 390                 395                 400

Lys Val Ser Asn Asp Ala Lys Arg Tyr Thr Arg Arg Pro Leu Val Val
                405                 410                 415

Val Tyr Tyr Ser Val Asp Phe Ser Phe Asp Tyr Arg Ala Ala Thr Gln
            420                 425                 430

Phe Trp Arg Ser Lys Val Leu Glu Val Ala Lys Asp Phe Pro Glu Tyr
        435                 440                 445

Thr Phe Ala Ile Ala Asp Glu Glu Asp Tyr Ala Gly Glu Val Lys Asp
    450                 455                 460

Leu Gly Leu Ser Glu Ser Gly Glu Asp Val Asn Ala Ala Ile Leu Asp
465                 470                 475                 480

Glu Ser Gly Lys Lys Phe Ala Met Glu Pro Glu Glu Phe Asp Ser Asp
                485                 490                 495

Thr Leu Arg Glu Phe Val Thr Ala Phe Lys Lys Gly Lys Leu Lys Pro
            500                 505                 510

Val Ile Lys Ser Gln Pro Val Pro Lys Asn Asn Lys Gly Pro Val Lys
        515                 520                 525

Val Val Val Gly Lys Thr Phe Asp Ser Ile Val Met Asp Pro Lys Lys
    530                 535                 540

Asp Val Leu Ile Glu Phe Tyr Ala Pro Trp Cys Gly His Cys Lys Gln
545                 550                 555                 560
```

```
Leu Glu Pro Val Tyr Asn Ser Leu Ala Lys Lys Tyr Lys Gly Gln Lys
                565                 570                 575

Gly Leu Val Ile Ala Lys Met Asp Ala Thr Ala Asn Asp Val Pro Ser
            580                 585                 590

Asp Arg Tyr Lys Val Glu Gly Phe Pro Thr Ile Tyr Phe Ala Pro Ser
        595                 600                 605

Gly Asp Lys Lys Asn Pro Val Lys Phe Glu Gly Gly Asp Arg Asp Leu
    610                 615                 620

Glu His Leu Ser Lys Phe Ile Glu Glu His Ala Thr Lys Leu Ser Arg
625                 630                 635                 640

Thr Lys Glu Glu Leu
                645

<210> 3
<211> 994
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (25)..(516)

<400> 3
tgctggccag cacctcgagg gaag atg gcg gac gag gag aag ctg ccg ccc    51
                           Met Ala Asp Glu Glu Lys Leu Pro Pro
                             1               5

ggc tgg gag aag cgc atg agc cgc agc tca ggc cga gtg tac tac ttc   99
Gly Trp Glu Lys Arg Met Ser Arg Ser Ser Gly Arg Val Tyr Tyr Phe
 10                  15                  20                  25

aac cac atc act aac gcc agc cag tgg gag cgg ccc agc ggc aac agc   147
Asn His Ile Thr Asn Ala Ser Gln Trp Glu Arg Pro Ser Gly Asn Ser
                30                  35                  40

agc agt ggt ggc aaa aac ggg cag ggg gag cct gcc agg gtc cgc tgc   195
Ser Ser Gly Gly Lys Asn Gly Gln Gly Glu Pro Ala Arg Val Arg Cys
            45                  50                  55

tcg cac ctg ctg gtg aag cac agc cag tca cgg cgg ccc tcg tcc tgg   243
Ser His Leu Leu Val Lys His Ser Gln Ser Arg Arg Pro Ser Ser Trp
        60                  65                  70

cgg cag gag aag atc acc cgg acc aag gag gag gcc ctg gag ctg atc   291
Arg Gln Glu Lys Ile Thr Arg Thr Lys Glu Glu Ala Leu Glu Leu Ile
    75                  80                  85

aac ggc tac atc cag aag atc aag tcg gga gag gag gac ttt gag tct   339
Asn Gly Tyr Ile Gln Lys Ile Lys Ser Gly Glu Glu Asp Phe Glu Ser
 90                  95                  100                 105
```

```
ctg gcc tca cag ttc agc gac tgc agc tca gcc aag gcc agg gga gac   387
Leu Ala Ser Gln Phe Ser Asp Cys Ser Ser Ala Lys Ala Arg Gly Asp
                110                 115                 120

ctg ggt gcc ttc agc aga ggt cag atg cag aag cca ttt gaa gac gcc   435
Leu Gly Ala Phe Ser Arg Gly Gln Met Gln Lys Pro Phe Glu Asp Ala
            125                 130                 135

tcg ttt gcg ctg cgg acg ggg gag atg agc ggg ccc gtg ttc acg gat   483
Ser Phe Ala Leu Arg Thr Gly Glu Met Ser Gly Pro Val Phe Thr Asp
        140                 145                 150

tcc ggc atc cac atc atc ctc cgc act gag tga gggtggggag cccaggcctg 536
Ser Gly Ile His Ile Ile Leu Arg Thr Glu
    155                 160

gcctcggggc agggcagggc ggctaggccg gccagctccc ccttgcccgc cagccagtgg 596

ccgaaccccc cactccctgc caccgtcaca cagtatttat tgttcccaca atggctggga 656

gggggccctt ccagattggg ggccctgggg tccccactcc ctgtccatcc ccagttgggg 716

ctgcgaccgc cagattctcc cttaaggaat tgacttcagc aggggtggga ggctcccaga 776

cccagggcag tgtggtggga ggggtgttcc aaagagaagg cctggtcagc agagccgccc 836

cgtgtccccc caggtgctgg aggcagactc gagggccgaa ttgtttctag ttaggccacg 896

ctcctctgtt cagtcgcaaa ggtgaacact catgcggcag ccatgggccc tctgagcaac 956

tgtgcagacc ctttcacccc caattaaacc cagaacca                         994


<210> 4
<211> 164
<212> PRT
<213> Homo sapiens

<400> 4
Met Ala Asp Glu Glu Lys Leu Pro Pro Gly Trp Glu Lys Arg Met Ser
  1               5                  10                  15

Arg Ser Ser Gly Arg Val Tyr Tyr Phe Asn His Ile Thr Asn Ala Ser
             20                  25                  30

Gln Trp Glu Arg Pro Ser Gly Asn Ser Ser Ser Gly Gly Lys Asn Gly
         35                  40                  45

Gln Gly Glu Pro Ala Arg Val Arg Cys Ser His Leu Leu Val Lys His
     50                  55                  60

Ser Gln Ser Arg Arg Pro Ser Ser Trp Arg Gln Glu Lys Ile Thr Arg
 65                  70                  75                  80
```

```
Thr Lys Glu Glu Ala Leu Glu Leu Ile Asn Gly Tyr Ile Gln Lys Ile
                85                  90                  95

Lys Ser Gly Glu Glu Asp Phe Glu Ser Leu Ala Ser Gln Phe Ser Asp
            100                 105                 110

Cys Ser Ser Ala Lys Ala Arg Gly Asp Leu Gly Ala Phe Ser Arg Gly
        115                 120                 125

Gln Met Gln Lys Pro Phe Glu Asp Ala Ser Phe Ala Leu Arg Thr Gly
    130                 135                 140

Glu Met Ser Gly Pro Val Phe Thr Asp Ser Gly Ile His Ile Ile Leu
145                 150                 155                 160

Arg Thr Glu
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<210> 5
<211> 2545
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (40)..(417)

<400> 5

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atccaataca ggagtgactt ggaactccat tctatcact atg aag aaa agt ggt    54
                                          Met Lys Lys Ser Gly
                                            1               5

gtt ctt ttc ctc ttg ggc atc atc ttg ctg gtt ctg att gga gtg caa   102
Val Leu Phe Leu Leu Gly Ile Ile Leu Leu Val Leu Ile Gly Val Gln
                10                  15                  20

gga acc cca gta gtg aga aag ggt cgc tgt tcc tgc atc agc acc aac   150
Gly Thr Pro Val Val Arg Lys Gly Arg Cys Ser Cys Ile Ser Thr Asn
            25                  30                  35

caa ggg act atc cac cta caa tcc ttg aaa gac ctt aaa caa ttt gcc   198
Gln Gly Thr Ile His Leu Gln Ser Leu Lys Asp Leu Lys Gln Phe Ala
        40                  45                  50

cca agc cct tcc tgc gag aaa att gaa atc att gct aca ctg aag aat   246
Pro Ser Pro Ser Cys Glu Lys Ile Glu Ile Ile Ala Thr Leu Lys Asn
    55                  60                  65

gga gtt caa aca tgt cta aac cca gat tca gca gat gtg aag gaa ctg   294
Gly Val Gln Thr Cys Leu Asn Pro Asp Ser Ala Asp Val Lys Glu Leu
70                  75                  80                  85

att aaa aag tgg gag aaa cag gtc agc caa aag aaa aag caa aag aat   342
Ile Lys Lys Trp Glu Lys Gln Val Ser Gln Lys Lys Lys Gln Lys Asn
                90                  95                  100
```

ggg aaa aaa cat caa aaa aag aaa gtt ctg aaa gtt cga aaa tct caa 390
Gly Lys Lys His Gln Lys Lys Lys Val Leu Lys Val Arg Lys Ser Gln
105 110 115

cgt tct cgt caa aag aag act aca taa gagaccactt caccaataag 437
Arg Ser Arg Gln Lys Lys Thr Thr
120 125

tattctgtgt taaaaatgtt ctattttaat tataccgcta tcattccaaa ggaggatggc 497

atataataca aaggcttatt aatttgacta gaaaatttaa aacattactc tgaaattgta 557

actaaagtta gaaagttgat tttaagaatc caaacgttaa gaattgttaa aggctatgat 617

tgtctttgtt cttctaccac ccaccagttg aatttcatca tgcttaaggc catgatttta 677

gcaataccca tgtctacaca gatgttcacc caaccacatc ccactcacaa cagctgcctg 737

gaagagcagc cctaggcttc cacgtactgc agcctccaga gagtatctga ggcacatgtc 797

agcaagtcct aagcctgtta gcatgctggt gagccaagca gtttgaaatt gagctggacc 857

tcaccaagct gctgtggcca tcaacctctg tatttgaatc agcctacagg cctcacacac 917

aatgtgtctg agagattcat gctgattgtt attgggtatc accactggag atcaccagtg 977

tgtggctttc agagcctcct ttctggcttt ggaagccatg tgattccatc ttgcccgctc 1037

aggctgacca ctttatttct ttttgttccc ctttgcttca ttcaagtcag ctcttctcca 1097

tcctaccaca atgcagtgcc tttcttctct ccagtgcacc tgtcatatgc tctgatttat 1157

ctgagtcaac tcctttctca tcttgtcccc aacaccccac agaagtgctt tcttctccca 1217

attcatcctc actcagtcca gcttagttca agtcctgcct cttaaataaa ccttttttgga 1277

cacacaaatt atcttaaaac tcctgtttca cttggttcag taccacatgg gtgaacactc 1337

aatggttaac taattcttgg gtgtttatcc tatctctcca accagattgt cagctccttg 1397

agggcaagag ccacagtata tttccctgtt tcttccacag tgcctaataa tactgtggaa 1457

ctaggtttta ataatttttt aattgatgtt gttatgggca ggatggcaac cagaccattg 1517

tctcagagca ggtgctggct ctttcctggc tactccatgt tggctagcct ctggtaacct 1577

cttacttatt atcttcagga cactcactac agggaccagg gatgatgcaa catccttgtc 1637

tttttatgac aggatgtttg ctcagcttct ccaacaataa gaagcacgtg gtaaaacact 1697

tgcggatatt ctggactgtt tttaaaaaat atacagttta ccgaaaatca tataatctta 1757

caatgaaaag gactttatag atcagccagt gaccaacctt ttcccaacca tacaaaaatt 1817

ccttttcccg aaggaaaagg gctttctcaa taagcctcag ctttctaaga tctaacaaga 1877

tagccaccga gatccttatc gaaactcatt ttaggcaaat atgagtttta ttgtccgttt 1937

acttgtttca gagtttgtat tgtgattatc aattaccaca ccatctccca tgaagaaagg 1997

gaacggtgaa gtactaagcg ctagaggaag cagccaagtc ggttagtgga agcatgattg 2057

gtgcccagtt agcctctgca ggatgtggaa acctccttcc aggggaggtt cagtgaattg 2117

tgtaggagag gttgtctgtg gccagaattt aaacctatac tcactttccc aaattgaatc 2177

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atctaatcat gaaactccct agttccttca tgtaacttcc ctgaaaaatc taagtgtttc 2297

ataaatttga gagtctgtga cccacttacc ttgcatctca caggtagaca gtatataact 2357

aacaaccaaa gactacatat tgtcactgac acacacgtta taatcattta tcatatatat 2417

acatacatgc atacactctc aaagcaaata atttttcact tcaaaacagt attgacttgt 2477

ataccttgta atttgaaata ttttctttgt taaaatagaa tggtatcaat aaatagacca 2537

ttaatcag 2545

<210> 6
<211> 126
<212> PRT
<213> Homo sapiens

<400> 6

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Met Lys Lys Ser Gly Val Leu Phe Leu Leu Gly Ile Ile Leu Leu Val
  1               5                  10                  15

Leu Ile Gly Val Gln Gly Thr Pro Val Val Arg Lys Gly Arg Cys Ser
            20                  25                  30

Cys Ile Ser Thr Asn Gln Gly Thr Ile His Leu Gln Ser Leu Lys Asp
        35                  40                  45

Leu Lys Gln Phe Ala Pro Ser Pro Ser Cys Glu Lys Ile Glu Ile Ile
    50                  55                  60

Ala Thr Leu Lys Asn Gly Val Gln Thr Cys Leu Asn Pro Asp Ser Ala
65                  70                  75                  80

Asp Val Lys Glu Leu Ile Lys Lys Trp Glu Lys Gln Val Ser Gln Lys
                85                  90                  95

Lys Lys Gln Lys Asn Gly Lys Lys His Gln Lys Lys Lys Val Leu Lys
            100                 105                 110

Val Arg Lys Ser Gln Arg Ser Arg Gln Lys Lys Thr Thr
        115                 120                 125
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<210> 7
<211> 1997
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (41)..(1834)

<400> 7
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Met Ala Ala Val Gln
1 5

gcg gcc gag gtg aaa gtg gat ggc agc gag ccg aaa ctg agc aag aat 103
Ala Ala Glu Val Lys Val Asp Gly Ser Glu Pro Lys Leu Ser Lys Asn
10 15 20

gag ctg aag aga cgc ctg aaa gct gag aag aaa gta gca gag aag gag 151
Glu Leu Lys Arg Arg Leu Lys Ala Glu Lys Lys Val Ala Glu Lys Glu
25 30 35

gcc aaa cag aaa gag ctc agt gag aaa cag cta agc caa gcc act gct 199
Ala Lys Gln Lys Glu Leu Ser Glu Lys Gln Leu Ser Gln Ala Thr Ala
40 45 50

gct gcc acc aac cac acc act gat aat ggt gtg ggt cct gag gaa gag 247
Ala Ala Thr Asn His Thr Thr Asp Asn Gly Val Gly Pro Glu Glu Glu
55 60 65

agc gtg gac cca aat caa tac tac aaa atc cgc agt caa gca att cat 295
Ser Val Asp Pro Asn Gln Tyr Tyr Lys Ile Arg Ser Gln Ala Ile His
70 75 80 85

cag ctg aag gtc aat ggg gaa gac cca tac cca cac aag ttc cat gta 343
Gln Leu Lys Val Asn Gly Glu Asp Pro Tyr Pro His Lys Phe His Val
90 95 100

gac atc tca ctc act gac ttc atc caa aaa tat agt cac ctg cag cct 391
Asp Ile Ser Leu Thr Asp Phe Ile Gln Lys Tyr Ser His Leu Gln Pro
105 110 115

ggg gat cac ctg act gac atc acc tta aag gtg gca ggt agg atc cat 439
Gly Asp His Leu Thr Asp Ile Thr Leu Lys Val Ala Gly Arg Ile His
120 125 130

gcc aaa aga gct tct ggg gga aag ctc atc ttc tat gat ctt cga gga 487
Ala Lys Arg Ala Ser Gly Gly Lys Leu Ile Phe Tyr Asp Leu Arg Gly
135 140 145

gag ggg gtg aag ttg caa gtc atg gcc aat tcc aga aat tat aaa tca 535
Glu Gly Val Lys Leu Gln Val Met Ala Asn Ser Arg Asn Tyr Lys Ser
150 155 160 165

```
gaa gaa gaa ttt att cat att aat aac aaa ctg cgt cgg gga gac ata   583
Glu Glu Glu Phe Ile His Ile Asn Asn Lys Leu Arg Arg Gly Asp Ile
                170                 175                 180

att gga gtt cag ggg aat cct ggt aaa acc aag aag ggt gag ctg agc   631
Ile Gly Val Gln Gly Asn Pro Gly Lys Thr Lys Lys Gly Glu Leu Ser
            185                 190                 195

atc att ccg tat gag atc aca ctg ctg tct ccc tgt ttg cat atg tta   679
Ile Ile Pro Tyr Glu Ile Thr Leu Leu Ser Pro Cys Leu His Met Leu
        200                 205                 210

cct cat ctt cac ttt ggg ctc aaa gac aag gaa aca agg tat cgc cag   727
Pro His Leu His Phe Gly Leu Lys Asp Lys Glu Thr Arg Tyr Arg Gln
    215                 220                 225

aga tac ttg gac ttg atc ctg aat gac ttt gtg agg cag aaa ttt atc   775
Arg Tyr Leu Asp Leu Ile Leu Asn Asp Phe Val Arg Gln Lys Phe Ile
230                 235                 240                 245

atc cgc tct aag atc atc aca tat ata aga agt ttc tta gat gag ctg   823
Ile Arg Ser Lys Ile Ile Thr Tyr Ile Arg Ser Phe Leu Asp Glu Leu
                250                 255                 260

gga ttc cta gag att gaa act ccc atg atg aac atc atc cca ggg gga   871
Gly Phe Leu Glu Ile Glu Thr Pro Met Met Asn Ile Ile Pro Gly Gly
            265                 270                 275

gcc gtg gcc aag cct ttc atc act tat cac aac gag ctg gac atg aac   919
Ala Val Ala Lys Pro Phe Ile Thr Tyr His Asn Glu Leu Asp Met Asn
        280                 285                 290

tta tat atg aga att gct cca gaa ctc tat cat aag atg ctt gtg gtt   967
Leu Tyr Met Arg Ile Ala Pro Glu Leu Tyr His Lys Met Leu Val Val
    295                 300                 305

ggt ggc atc gac cgg gtt tat gaa att gga cgc cag ttc cgg aat gag   1015
Gly Gly Ile Asp Arg Val Tyr Glu Ile Gly Arg Gln Phe Arg Asn Glu
310                 315                 320                 325

ggg att gat ttg acg cac aat cct gag ttc acc acc tgt gag ttc tac   1063
Gly Ile Asp Leu Thr His Asn Pro Glu Phe Thr Thr Cys Glu Phe Tyr
                330                 335                 340

atg gcc tat gca gac tat cac gat ctc atg gaa atc acg gag aag atg   1111
Met Ala Tyr Ala Asp Tyr His Asp Leu Met Glu Ile Thr Glu Lys Met
            345                 350                 355

gtt tca ggg atg gtg aag cat att aca ggc agt tac aag gtc acc tac   1159
Val Ser Gly Met Val Lys His Ile Thr Gly Ser Tyr Lys Val Thr Tyr
        360                 365                 370

cac cca gat ggc cca gag ggc caa gcc tac gat gtt gac ttc acc cca   1207
His Pro Asp Gly Pro Glu Gly Gln Ala Tyr Asp Val Asp Phe Thr Pro
    375                 380                 385
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ccc ttc cgg cga atc aac atg gta gaa gag ctt gag aaa gcc ctg ggg   1255
Pro Phe Arg Arg Ile Asn Met Val Glu Glu Leu Glu Lys Ala Leu Gly
390                 395                 400                 405

atg aag ctg cca gaa acg aac ctc ttt gaa act gaa gaa act cgc aaa   1303
Met Lys Leu Pro Glu Thr Asn Leu Phe Glu Thr Glu Glu Thr Arg Lys
                410                 415                 420

att ctt gat gat atc tgt gtg gca aaa gct gtt gaa tgc cct cca cct   1351
Ile Leu Asp Asp Ile Cys Val Ala Lys Ala Val Glu Cys Pro Pro Pro
            425                 430                 435

cgg acc aca gcc agg ctc ctt gac aag ctt gtt ggg gag ttc ctg gaa   1399
Arg Thr Thr Ala Arg Leu Leu Asp Lys Leu Val Gly Glu Phe Leu Glu
        440                 445                 450

gtg act tgc atc aat cct aca ttc atc tgt gat cac cca cag ata atg   1447
Val Thr Cys Ile Asn Pro Thr Phe Ile Cys Asp His Pro Gln Ile Met
    455                 460                 465

agc cct ttg gct aaa tgg cac cgc tct aaa gag ggt ctg act gag cgc   1495
Ser Pro Leu Ala Lys Trp His Arg Ser Lys Glu Gly Leu Thr Glu Arg
470                 475                 480                 485

ttt gag ctg ttt gtc atg aag aaa gag ata tgc aat gcg tat act gag   1543
Phe Glu Leu Phe Val Met Lys Lys Glu Ile Cys Asn Ala Tyr Thr Glu
                490                 495                 500

ctg aat gat ccc atg cgg cag cgg cag ctt ttt gaa gaa cag gcc aag   1591
Leu Asn Asp Pro Met Arg Gln Arg Gln Leu Phe Glu Glu Gln Ala Lys
            505                 510                 515

gcc aag gct gca ggt gat gat gag gcc atg ttc ata gat gaa aac ttc   1639
Ala Lys Ala Ala Gly Asp Asp Glu Ala Met Phe Ile Asp Glu Asn Phe
        520                 525                 530

tgt act gcc ctg gaa tat ggg ctg ccc ccc aca gct ggc tgg ggc atg   1687
Cys Thr Ala Leu Glu Tyr Gly Leu Pro Pro Thr Ala Gly Trp Gly Met
    535                 540                 545

ggc att gat cga gtc gcc atg ttt ctc acg gac tcc aac aac atc aag   1735
Gly Ile Asp Arg Val Ala Met Phe Leu Thr Asp Ser Asn Asn Ile Lys
550                 555                 560                 565

gaa gta ctt ctg ttt cct gcc atg aaa ccc gaa gac aag aag gag aat   1783
Glu Val Leu Leu Phe Pro Ala Met Lys Pro Glu Asp Lys Lys Glu Asn
                570                 575                 580

gta gca acc act gat aca ctg gaa agc aca aca gtt ggc act tct gtc   1831
Val Ala Thr Thr Asp Thr Leu Glu Ser Thr Thr Val Gly Thr Ser Val
            585                 590                 595

tag aaaataataa ttgcaagttg tataactcag gcgtctttgc atttctgcga       1884


aagatcaagg tctgcaaggg aattcttgtg tgctgctttc catttgacac cgcagttctg 1944
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ttcagccatc agaagagaga caaggaatta aaaatttctt tttaatcctg tta 1997

<210> 8
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<213> Homo sapiens

<400> 8

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Met Ala Ala Val Gln Ala Ala Glu Val Lys Val Asp Gly Ser Glu Pro
 1               5                  10                  15

Lys Leu Ser Lys Asn Glu Leu Lys Arg Arg Leu Lys Ala Glu Lys Lys
            20                  25                  30

Val Ala Glu Lys Glu Ala Lys Gln Lys Glu Leu Ser Glu Lys Gln Leu
        35                  40                  45

Ser Gln Ala Thr Ala Ala Ala Thr Asn His Thr Thr Asp Asn Gly Val
    50                  55                  60

Gly Pro Glu Glu Glu Ser Val Asp Pro Asn Gln Tyr Tyr Lys Ile Arg
65                  70                  75                  80

Ser Gln Ala Ile His Gln Leu Lys Val Asn Gly Glu Asp Pro Tyr Pro
                85                  90                  95

His Lys Phe His Val Asp Ile Ser Leu Thr Asp Phe Ile Gln Lys Tyr
            100                 105                 110

Ser His Leu Gln Pro Gly Asp His Leu Thr Asp Ile Thr Leu Lys Val
        115                 120                 125

Ala Gly Arg Ile His Ala Lys Arg Ala Ser Gly Gly Lys Leu Ile Phe
    130                 135                 140

Tyr Asp Leu Arg Gly Glu Gly Val Lys Leu Gln Val Met Ala Asn Ser
145                 150                 155                 160

Arg Asn Tyr Lys Ser Glu Glu Glu Phe Ile His Ile Asn Asn Lys Leu
                165                 170                 175

Arg Arg Gly Asp Ile Ile Gly Val Gln Gly Asn Pro Gly Lys Thr Lys
            180                 185                 190

Lys Gly Glu Leu Ser Ile Ile Pro Tyr Glu Ile Thr Leu Leu Ser Pro
        195                 200                 205

Cys Leu His Met Leu Pro His Leu His Phe Gly Leu Lys Asp Lys Glu
    210                 215                 220

Thr Arg Tyr Arg Gln Arg Tyr Leu Asp Leu Ile Leu Asn Asp Phe Val
225                 230                 235                 240
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Arg Gln Lys Phe Ile Ile Arg Ser Lys Ile Ile Thr Tyr Ile Arg Ser
                245                 250                 255

Phe Leu Asp Glu Leu Gly Phe Leu Glu Ile Glu Thr Pro Met Met Asn
            260                 265                 270

Ile Ile Pro Gly Gly Ala Val Ala Lys Pro Phe Ile Thr Tyr His Asn
        275                 280                 285

Glu Leu Asp Met Asn Leu Tyr Met Arg Ile Ala Pro Glu Leu Tyr His
    290                 295                 300

Lys Met Leu Val Val Gly Gly Ile Asp Arg Val Tyr Glu Ile Gly Arg
305                 310                 315                 320

Gln Phe Arg Asn Glu Gly Ile Asp Leu Thr His Asn Pro Glu Phe Thr
                325                 330                 335

Thr Cys Glu Phe Tyr Met Ala Tyr Ala Asp Tyr His Asp Leu Met Glu
            340                 345                 350

Ile Thr Glu Lys Met Val Ser Gly Met Val Lys His Ile Thr Gly Ser
        355                 360                 365

Tyr Lys Val Thr Tyr His Pro Asp Gly Pro Glu Gly Gln Ala Tyr Asp
    370                 375                 380

Val Asp Phe Thr Pro Pro Phe Arg Arg Ile Asn Met Val Glu Glu Leu
385                 390                 395                 400

Glu Lys Ala Leu Gly Met Lys Leu Pro Glu Thr Asn Leu Phe Glu Thr
                405                 410                 415

Glu Glu Thr Arg Lys Ile Leu Asp Asp Ile Cys Val Ala Lys Ala Val
            420                 425                 430

Glu Cys Pro Pro Pro Arg Thr Thr Ala Arg Leu Leu Asp Lys Leu Val
        435                 440                 445

Gly Glu Phe Leu Glu Val Thr Cys Ile Asn Pro Thr Phe Ile Cys Asp
    450                 455                 460

His Pro Gln Ile Met Ser Pro Leu Ala Lys Trp His Arg Ser Lys Glu
465                 470                 475                 480

Gly Leu Thr Glu Arg Phe Glu Leu Phe Val Met Lys Lys Glu Ile Cys
                485                 490                 495

Asn Ala Tyr Thr Glu Leu Asn Asp Pro Met Arg Gln Arg Gln Leu Phe
            500                 505                 510

Glu Glu Gln Ala Lys Ala Lys Ala Ala Gly Asp Asp Glu Ala Met Phe
        515                 520                 525

Ile Asp Glu Asn Phe Cys Thr Ala Leu Glu Tyr Gly Leu Pro Pro Thr
    530                 535                 540
```

```
Ala Gly Trp Gly Met Gly Ile Asp Arg Val Ala Met Phe Leu Thr Asp
545                 550                 555                 560

Ser Asn Asn Ile Lys Glu Val Leu Leu Phe Pro Ala Met Lys Pro Glu
                565                 570                 575

Asp Lys Lys Glu Asn Val Ala Thr Thr Asp Thr Leu Glu Ser Thr Thr
            580                 585                 590

Val Gly Thr Ser Val
        595
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<210> 9
<211> 1172
<212> DNA
<213> Homo sapiens

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<222> (67)..(363)

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agcacc atg aat caa act gcg att ctg att tgc tgc ctt atc ttt ctg    108
       Met Asn Gln Thr Ala Ile Leu Ile Cys Cys Leu Ile Phe Leu
         1               5                  10

act cta agt ggc att caa gga gta cct ctc tct aga acc gta cgc tgt   156
Thr Leu Ser Gly Ile Gln Gly Val Pro Leu Ser Arg Thr Val Arg Cys
 15                  20                  25                  30

acc tgc atc agc att agt aat caa cct gtt aat cca agg tct tta gaa   204
Thr Cys Ile Ser Ile Ser Asn Gln Pro Val Asn Pro Arg Ser Leu Glu
                35                  40                  45

aaa ctt gaa att att cct gca agc caa ttt tgt cca cgt gtt gag atc   252
Lys Leu Glu Ile Ile Pro Ala Ser Gln Phe Cys Pro Arg Val Glu Ile
            50                  55                  60

att gct aca atg aaa aag aag ggt gag aag aga tgt ctg aat cca gaa   300
Ile Ala Thr Met Lys Lys Lys Gly Glu Lys Arg Cys Leu Asn Pro Glu
        65                  70                  75

tcg aag gcc atc aag aat tta ctg aaa gca gtt agc aag gaa atg tct   348
Ser Lys Ala Ile Lys Asn Leu Leu Lys Ala Val Ser Lys Glu Met Ser
    80                  85                  90

aaa aga tct cct taa aaccagaggg gagcaaaatc gatgcagtgc ttccaaggat   403
Lys Arg Ser Pro
 95

ggaccacaca gaggctgcct ctcccatcac ttccctacat ggagtatatg tcaagccata 463
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attgttctta gtttgcagtt acactaaaag gtgaccaatg atggtcacca aatcagctgc 523

tactactcct gtaggaaggt taatgttcat catcctaagc tattcagtaa taactctacc 583

ctggcactat aatgtaagct ctactgaggt gctatgttct tagtggatgt tctgaccctg 643

cttcaaatat ttccctcacc tttcccatct tccaagggta ctaaggaatc tttctgcttt 703

ggggtttatc agaattctca gaatctcaaa taactaaaag gtatgcaatc aaatctgctt 763

tttaaagaat gctctttact tcatggactt ccactgccat cctcccaagg ggcccaaatt 823

ctttcagtgg ctacctacat acaattccaa acacatacag gaaggtagaa atatctgaaa 883

atgtatgtgt aagtattctt atttaatgaa agactgtaca aagtataagt cttagatgta 943

tatatttcct atattgtttt cagtgtacat ggaataacat gtaattaagt actatgtatc 1003

aatgagtaac aggaaaattt taaaaataca gatagatata tgctctgcat gttacataag 1063

ataaatgtgc tgaatggttt tcaaataaaa atgaggtact ctcctggaaa tattaagaaa 1123

gactatctaa atgttgaaag atcaaaaggt taataaagta attataact 1172

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<213> Homo sapiens

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Met Asn Gln Thr Ala Ile Leu Ile Cys Cys Leu Ile Phe Leu Thr Leu
1 5 10 15

Ser Gly Ile Gln Gly Val Pro Leu Ser Arg Thr Val Arg Cys Thr Cys
20 25 30

Ile Ser Ile Ser Asn Gln Pro Val Asn Pro Arg Ser Leu Glu Lys Leu
35 40 45

Glu Ile Ile Pro Ala Ser Gln Phe Cys Pro Arg Val Glu Ile Ile Ala
50 55 60

Thr Met Lys Lys Lys Gly Glu Lys Arg Cys Leu Asn Pro Glu Ser Lys
65 70 75 80

Ala Ile Lys Asn Leu Leu Lys Ala Val Ser Lys Glu Met Ser Lys Arg
85 90 95

Ser Pro

<210> 11
<211> 770
<212> DNA

<213> Homo sapiens

<220>
<221> CDS
<222> (44)..(574)

<400> 11

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cagcaagcga cctgtcaggc ggccgtggac tcagactccg gag atg aag ccc ctg   55
                                                 Met Lys Pro Leu
                                                   1

ctc ctg gcc gtc agc ctt ggc ctc att gct gcc ctg cag gcc cac cac   103
Leu Leu Ala Val Ser Leu Gly Leu Ile Ala Ala Leu Gln Ala His His
  5                  10                  15                  20

ctc ctg gct tca gac gag gag att cag gat gtg tca ggg acg tgg tat   151
Leu Leu Ala Ser Asp Glu Glu Ile Gln Asp Val Ser Gly Thr Trp Tyr
                 25                  30                  35

ctg aag gcc atg act gtg gac agg gag ttc cct gag atg aat ctg gaa   199
Leu Lys Ala Met Thr Val Asp Arg Glu Phe Pro Glu Met Asn Leu Glu
             40                  45                  50

tcg gtg aca ccc atg acc ctc acg acc ctg gaa ggg ggc aac ctg gaa   247
Ser Val Thr Pro Met Thr Leu Thr Thr Leu Glu Gly Gly Asn Leu Glu
         55                  60                  65

gcc aag gtc acc atg ctg ata agt ggc cgg tgc cag gag gtg aag gcc   295
Ala Lys Val Thr Met Leu Ile Ser Gly Arg Cys Gln Glu Val Lys Ala
     70                  75                  80

gtc ctg gag aaa act gac gag ccg gga aaa tac acg gcc gac ggg ggc   343
Val Leu Glu Lys Thr Asp Glu Pro Gly Lys Tyr Thr Ala Asp Gly Gly
 85                  90                  95                  100

aag cac gtg gca tac atc atc agg tcg cac gtg aag gac cac tac atc   391
Lys His Val Ala Tyr Ile Ile Arg Ser His Val Lys Asp His Tyr Ile
                105                 110                 115

ttt tac tgt gag ggc gag ctg cac ggg aag ccg gtc cga ggg gtg aag   439
Phe Tyr Cys Glu Gly Glu Leu His Gly Lys Pro Val Arg Gly Val Lys
            120                 125                 130

ctc gtg ggc aga gac ccc aag aac aac ctg gaa gcc ttg gag gac ttt   487
Leu Val Gly Arg Asp Pro Lys Asn Asn Leu Glu Ala Leu Glu Asp Phe
        135                 140                 145

gag aaa gcc gca gga gcc cgc gga ctc agc acg gag agc atc ctc atc   535
Glu Lys Ala Ala Gly Ala Arg Gly Leu Ser Thr Glu Ser Ile Leu Ile
    150                 155                 160

ccc agg cag agc gaa acc tgc tct cca ggg agc gat tag gggcagggga   584
Pro Arg Gln Ser Glu Thr Cys Ser Pro Gly Ser Asp
165                 170                 175

caccttggct cctcagcagc caaggacggc accatccagc acctccgtca ttcacaggga 644
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catggaaaaa gctccccacc cctgcagaac gcggctggct gcacccttc ctaccacccc 704

ccgccttccc cctgccctgc gccccctctc ctggttctcc ataaagagct tcagcagtta 764

aaaaaa 770

<210> 12
<211> 177
<212> PRT
<213> Homo sapiens

<400> 12
Met Lys Pro Leu Leu Leu Ala Val Ser Leu Gly Leu Ile Ala Ala Leu
1 5 10 15

Gln Ala His His Leu Leu Ala Ser Asp Glu Glu Ile Gln Asp Val Ser
20 25 30

Gly Thr Trp Tyr Leu Lys Ala Met Thr Val Asp Arg Glu Phe Pro Glu
35 40 45

Met Asn Leu Glu Ser Val Thr Pro Met Thr Leu Thr Thr Leu Glu Gly
50 55 60

Gly Asn Leu Glu Ala Lys Val Thr Met Leu Ile Ser Gly Arg Cys Gln
65 70 75 80

Glu Val Lys Ala Val Leu Glu Lys Thr Asp Glu Pro Gly Lys Tyr Thr
85 90 95

Ala Asp Gly Gly Lys His Val Ala Tyr Ile Ile Arg Ser His Val Lys
100 105 110

Asp His Tyr Ile Phe Tyr Cys Glu Gly Glu Leu His Gly Lys Pro Val
115 120 125

Arg Gly Val Lys Leu Val Gly Arg Asp Pro Lys Asn Asn Leu Glu Ala
130 135 140

Leu Glu Asp Phe Glu Lys Ala Ala Gly Ala Arg Gly Leu Ser Thr Glu
145 150 155 160

Ser Ile Leu Ile Pro Arg Gln Ser Glu Thr Cys Ser Pro Gly Ser Asp
165 170 175

<210> 13
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<213> Homo sapiens

<220>
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<222> (1)..(2283)

<400> 13

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atg gcc ggg cag cag ttc cag tac gat gac agt ggg aac acc ttc ttc   48
Met Ala Gly Gln Gln Phe Gln Tyr Asp Asp Ser Gly Asn Thr Phe Phe
  1               5                  10                  15

tac ttc ctc acc tcc ttc gtg ggg ctc atc gtg atc ccg gcg aca tac   96
Tyr Phe Leu Thr Ser Phe Val Gly Leu Ile Val Ile Pro Ala Thr Tyr
             20                  25                  30

tac ctc tgg ccc cga gat cag aat gcc gag caa att cga tta aag aat   144
Tyr Leu Trp Pro Arg Asp Gln Asn Ala Glu Gln Ile Arg Leu Lys Asn
         35                  40                  45

atc aga aaa gta tat gga agg tgt atg tgg tat cgt tta cgg tta tta   192
Ile Arg Lys Val Tyr Gly Arg Cys Met Trp Tyr Arg Leu Arg Leu Leu
     50                  55                  60

aaa ccc cag cca aat att att cct aca gta aag aaa ata gtt ctg ctt   240
Lys Pro Gln Pro Asn Ile Ile Pro Thr Val Lys Lys Ile Val Leu Leu
 65                  70                  75                  80

gca gga tgg gca ttg ttc tta ttc ctt gca tat aaa gtt tcc aaa aca   288
Ala Gly Trp Ala Leu Phe Leu Phe Leu Ala Tyr Lys Val Ser Lys Thr
                 85                  90                  95

gac cga gaa tac caa gaa tac aat cct tat gaa gta tta aat ttg gat   336
Asp Arg Glu Tyr Gln Glu Tyr Asn Pro Tyr Glu Val Leu Asn Leu Asp
            100                 105                 110

cct gga gcc aca gta gca gaa att aaa aaa caa tat cgt ttg ctg tca   384
Pro Gly Ala Thr Val Ala Glu Ile Lys Lys Gln Tyr Arg Leu Leu Ser
        115                 120                 125

ctt aaa tat cat cca gat aaa gga ggt gat gag gtt atg ttc atg agg   432
Leu Lys Tyr His Pro Asp Lys Gly Gly Asp Glu Val Met Phe Met Arg
    130                 135                 140

ata gca aaa gct tat gct gct tta acg gat gaa gag tcc cgg aaa aat   480
Ile Ala Lys Ala Tyr Ala Ala Leu Thr Asp Glu Glu Ser Arg Lys Asn
145                 150                 155                 160

tgg gaa gaa ttt gga aat cca gat ggg cct caa gcc aca agc ttt gga   528
Trp Glu Glu Phe Gly Asn Pro Asp Gly Pro Gln Ala Thr Ser Phe Gly
                165                 170                 175

att gcc ctg cca gct tgg ata gtt gac cag aaa aat tca att ctg gtt   576
Ile Ala Leu Pro Ala Trp Ile Val Asp Gln Lys Asn Ser Ile Leu Val
            180                 185                 190

tta ctt gta tat gga ttg gca ttt atg gtt atc ctt cca gtt gtt gtg   624
Leu Leu Val Tyr Gly Leu Ala Phe Met Val Ile Leu Pro Val Val Val
        195                 200                 205
```

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ggc tct tgg tgg tat cgc tca ata cgc tat agt gga gac cag att cta   672
Gly Ser Trp Trp Tyr Arg Ser Ile Arg Tyr Ser Gly Asp Gln Ile Leu
    210                 215                 220

ata cgc aca aca cag att tat aca tac ttt gtt tat aaa acc cga aat   720
Ile Arg Thr Thr Gln Ile Tyr Thr Tyr Phe Val Tyr Lys Thr Arg Asn
225                 230                 235                 240

atg gat atg aaa cgt ctt atc atg gtt ttg gct gga gct tct gaa ttt   768
Met Asp Met Lys Arg Leu Ile Met Val Leu Ala Gly Ala Ser Glu Phe
                245                 250                 255

gat cct cag tat aat aaa gat gcc aca agc aga cca acg gat aat att   816
Asp Pro Gln Tyr Asn Lys Asp Ala Thr Ser Arg Pro Thr Asp Asn Ile
            260                 265                 270

cta ata cca cag cta atc aga gaa att ggc agc att aat tta aag aag   864
Leu Ile Pro Gln Leu Ile Arg Glu Ile Gly Ser Ile Asn Leu Lys Lys
        275                 280                 285

aat gag cct cca ctt acc tgc cca tat agc ctg aag gcc aga gtt ctt   912
Asn Glu Pro Pro Leu Thr Cys Pro Tyr Ser Leu Lys Ala Arg Val Leu
    290                 295                 300

tta ctg tct cat ctt gct aga atg aaa att cct gag acc ctt gaa gaa   960
Leu Leu Ser His Leu Ala Arg Met Lys Ile Pro Glu Thr Leu Glu Glu
305                 310                 315                 320

gat cag caa ttc atg cta aaa aag tgt cct gcc cta ctt caa gaa atg   1008
Asp Gln Gln Phe Met Leu Lys Lys Cys Pro Ala Leu Leu Gln Glu Met
                325                 330                 335

gtt aat gta atc tgc caa cta ata gta atg gcc cgg aac cgt gaa gaa   1056
Val Asn Val Ile Cys Gln Leu Ile Val Met Ala Arg Asn Arg Glu Glu
            340                 345                 350

agg gag ttt cgt gct cca act ttg gca tcc cta gaa aac tgc atg aag   1104
Arg Glu Phe Arg Ala Pro Thr Leu Ala Ser Leu Glu Asn Cys Met Lys
        355                 360                 365

ctt tct cag atg gcc gtt cag gga ctt cag caa ttt aag tct ccc ctt   1152
Leu Ser Gln Met Ala Val Gln Gly Leu Gln Gln Phe Lys Ser Pro Leu
    370                 375                 380

ctg cag ctc cct cat att gaa gag gac aat ctt aga cgg gtt tct aat   1200
Leu Gln Leu Pro His Ile Glu Glu Asp Asn Leu Arg Arg Val Ser Asn
385                 390                 395                 400

cat aag aag tat aaa att aaa act atc cag gat ttg gtg agt tta aaa   1248
His Lys Lys Tyr Lys Ile Lys Thr Ile Gln Asp Leu Val Ser Leu Lys
                405                 410                 415

gaa tca gat cgt cac act cta ctg cac ttc ctt gaa gat gaa aaa tat   1296
Glu Ser Asp Arg His Thr Leu Leu His Phe Leu Glu Asp Glu Lys Tyr
            420                 425                 430
```

```
gaa gag gtt atg gct gtc ctt ggg agt ttt cca tat gtg acc atg gat   1344
Glu Glu Val Met Ala Val Leu Gly Ser Phe Pro Tyr Val Thr Met Asp
        435                 440                 445

ata aaa tca cag gtg tta gat gat gaa gat agc aac aac atc aca gta   1392
Ile Lys Ser Gln Val Leu Asp Asp Glu Asp Ser Asn Asn Ile Thr Val
    450                 455                 460

gga tcc tta gtt aca gtg ttg gtt aag ttg aca agg caa aca atg gct   1440
Gly Ser Leu Val Thr Val Leu Val Lys Leu Thr Arg Gln Thr Met Ala
465                 470                 475                 480

gaa gta ttt gaa aag gag cag tcc atc tgt gct gca gag gaa cag cca   1488
Glu Val Phe Glu Lys Glu Gln Ser Ile Cys Ala Ala Glu Glu Gln Pro
                485                 490                 495

gca gaa gat ggg cag ggt gaa act aac aag aac agg aca aaa gga gga   1536
Ala Glu Asp Gly Gln Gly Glu Thr Asn Lys Asn Arg Thr Lys Gly Gly
            500                 505                 510

tgg caa cag aag agt aaa gga ccc aag aaa act gct aaa tca aaa aaa   1584
Trp Gln Gln Lys Ser Lys Gly Pro Lys Lys Thr Ala Lys Ser Lys Lys
        515                 520                 525

aag aaa cct tta aaa aaa aaa cct aca cct gtg cta tta cca cag tca   1632
Lys Lys Pro Leu Lys Lys Lys Pro Thr Pro Val Leu Leu Pro Gln Ser
    530                 535                 540

aag caa cag aaa caa aag cag gca aat gga gtc gtt ggg aat gaa gct   1680
Lys Gln Gln Lys Gln Lys Gln Ala Asn Gly Val Val Gly Asn Glu Ala
545                 550                 555                 560

gca gta aag gaa gat gaa gaa gaa gtt tca gat aag ggc agt gat tct   1728
Ala Val Lys Glu Asp Glu Glu Glu Val Ser Asp Lys Gly Ser Asp Ser
                565                 570                 575

gaa gaa gaa gaa acc aat aga gat tcc caa agt gag aaa gat gat ggt   1776
Glu Glu Glu Glu Thr Asn Arg Asp Ser Gln Ser Glu Lys Asp Asp Gly
            580                 585                 590

agt gac aga gac tct gat aga gag caa gat gaa aaa caa aac aaa gat   1824
Ser Asp Arg Asp Ser Asp Arg Glu Gln Asp Glu Lys Gln Asn Lys Asp
        595                 600                 605

gat gaa gca gag tgg caa gaa tta caa caa agc ata cag cga aaa gag   1872
Asp Glu Ala Glu Trp Gln Glu Leu Gln Gln Ser Ile Gln Arg Lys Glu
    610                 615                 620

aga gct cta ttg gaa acc aaa tca aaa ata aca cat cct gtg tat agc   1920
Arg Ala Leu Leu Glu Thr Lys Ser Lys Ile Thr His Pro Val Tyr Ser
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ctt tac ttt cct gag gaa aaa caa gaa tgg tgg tgg ctt tac att gca   1968
Leu Tyr Phe Pro Glu Glu Lys Gln Glu Trp Trp Trp Leu Tyr Ile Ala
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gat agg aag gag cag aca tta ata tcc atg cca tat cat gtg tgt acg   2016
Asp Arg Lys Glu Gln Thr Leu Ile Ser Met Pro Tyr His Val Cys Thr
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ctg aaa gat aca gag gag gta gag ctg aag ttt cct gca cca ggc aag   2064
Leu Lys Asp Thr Glu Glu Val Glu Leu Lys Phe Pro Ala Pro Gly Lys
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cct gga aat tat cag tat act gtg ttt ctg aga tca gac tcc tat atg   2112
Pro Gly Asn Tyr Gln Tyr Thr Val Phe Leu Arg Ser Asp Ser Tyr Met
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ggt ttg gat cag att aaa cca ttg aag ttg gaa gtt cat gag gct aag   2160
Gly Leu Asp Gln Ile Lys Pro Leu Lys Leu Glu Val His Glu Ala Lys
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cct gtg cca gaa aat cac cca cag tgg gat aca gca ata gag ggg gat   2208
Pro Val Pro Glu Asn His Pro Gln Trp Asp Thr Ala Ile Glu Gly Asp
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gaa gac cag gag gac agt gag ggc ttt gaa gat agc ttt gag gaa gaa   2256
Glu Asp Gln Glu Asp Ser Glu Gly Phe Glu Asp Ser Phe Glu Glu Glu
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Tyr Leu Trp Pro Arg Asp Gln Asn Ala Glu Gln Ile Arg Leu Lys Asn
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Ile Arg Lys Val Tyr Gly Arg Cys Met Trp Tyr Arg Leu Arg Leu Leu
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Lys Pro Gln Pro Asn Ile Ile Pro Thr Val Lys Lys Ile Val Leu Leu
65                  70                  75                  80

Ala Gly Trp Ala Leu Phe Leu Phe Leu Ala Tyr Lys Val Ser Lys Thr
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Asp Arg Glu Tyr Gln Glu Tyr Asn Pro Tyr Glu Val Leu Asn Leu Asp
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Ile Ala Lys Ala Tyr Ala Ala Leu Thr Asp Glu Glu Ser Arg Lys Asn
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Trp Glu Glu Phe Gly Asn Pro Asp Gly Pro Gln Ala Thr Ser Phe Gly
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Ile Ala Leu Pro Ala Trp Ile Val Asp Gln Lys Asn Ser Ile Leu Val
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Leu Leu Val Tyr Gly Leu Ala Phe Met Val Ile Leu Pro Val Val Val
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Gly Ser Trp Trp Tyr Arg Ser Ile Arg Tyr Ser Gly Asp Gln Ile Leu
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Ile Arg Thr Thr Gln Ile Tyr Thr Tyr Phe Val Tyr Lys Thr Arg Asn
225                 230                 235                 240

Met Asp Met Lys Arg Leu Ile Met Val Leu Ala Gly Ala Ser Glu Phe
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Asp Pro Gln Tyr Asn Lys Asp Ala Thr Ser Arg Pro Thr Asp Asn Ile
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Leu Ile Pro Gln Leu Ile Arg Glu Ile Gly Ser Ile Asn Leu Lys Lys
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Asn Glu Pro Pro Leu Thr Cys Pro Tyr Ser Leu Lys Ala Arg Val Leu
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Leu Leu Ser His Leu Ala Arg Met Lys Ile Pro Glu Thr Leu Glu Glu
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Asp Gln Gln Phe Met Leu Lys Lys Cys Pro Ala Leu Leu Gln Glu Met
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Val Asn Val Ile Cys Gln Leu Ile Val Met Ala Arg Asn Arg Glu Glu
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Arg Glu Phe Arg Ala Pro Thr Leu Ala Ser Leu Glu Asn Cys Met Lys
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Leu Ser Gln Met Ala Val Gln Gly Leu Gln Gln Phe Lys Ser Pro Leu
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Leu Gln Leu Pro His Ile Glu Glu Asp Asn Leu Arg Arg Val Ser Asn
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His Lys Lys Tyr Lys Ile Lys Thr Ile Gln Asp Leu Val Ser Leu Lys
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Glu Ser Asp Arg His Thr Leu Leu His Phe Leu Glu Asp Glu Lys Tyr
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Glu Glu Val Met Ala Val Leu Gly Ser Phe Pro Tyr Val Thr Met Asp
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Ile Lys Ser Gln Val Leu Asp Asp Glu Asp Ser Asn Asn Ile Thr Val
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Gly Ser Leu Val Thr Val Leu Val Lys Leu Thr Arg Gln Thr Met Ala
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Glu Val Phe Glu Lys Glu Gln Ser Ile Cys Ala Ala Glu Glu Gln Pro
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Ala Glu Asp Gly Gln Gly Glu Thr Asn Lys Asn Arg Thr Lys Gly Gly
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Trp Gln Gln Lys Ser Lys Gly Pro Lys Lys Thr Ala Lys Ser Lys Lys
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Asp Glu Ala Glu Trp Gln Glu Leu Gln Gln Ser Ile Gln Arg Lys Glu
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Arg Ala Leu Leu Glu Thr Lys Ser Lys Ile Thr His Pro Val Tyr Ser
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Leu Tyr Phe Pro Glu Glu Lys Gln Glu Trp Trp Trp Leu Tyr Ile Ala
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Asp Arg Lys Glu Gln Thr Leu Ile Ser Met Pro Tyr His Val Cys Thr
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Ile Leu Pro Gln Asp Leu Glu Arg Ala Gly Leu Val
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Gly Lys Thr Gln Gly Ser Glu Thr Ala Gly Pro Pro Lys Lys Lys Arg
        35                  40                  45

Lys Lys Thr Gln Lys Lys Phe Arg Lys Arg Glu Glu Lys Ala Ala Glu
    50                  55                  60

His Lys Ala Lys Ser Leu Gly Glu Lys Ser Pro Ala Ala Ser Gly Ala
65                  70                  75                  80

Arg Arg Pro Glu Ala Ala Lys Glu Glu Ala Ala Trp Ala Ser Ser Ser
                85                  90                  95

Ala Gly Asn Pro Ala Asn Gly Leu Ala Thr Glu Pro Glu Ser Val Phe
            100                 105                 110

Ala Leu Asp Val Leu Arg Gln Arg Leu His Glu Lys Ile Gln Glu Ala
        115                 120                 125

Arg Gly Gln Gly Ser Ala Lys Glu Leu Ser Pro Ala Ala Leu Glu Lys
    130                 135                 140

Arg Arg Arg Arg Lys Gln Glu Arg Asp Arg Lys Lys Arg Lys Arg Lys
145                 150                 155                 160

Glu Leu Arg Ala Lys Glu Lys Ala Arg Lys Ala Glu Glu Ala Thr Glu
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Ala Gln Glu Val Val Glu Ala Thr Pro Glu Gly Ala Cys Thr Glu Pro
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Arg Glu Pro Pro Gly Leu Ile Phe Asn Lys Val Glu Val Ser Glu Asp
195 200 205

Glu Pro Ala Ser Lys Ala Gln Arg Arg Lys Glu Lys Arg Gln Arg Val
210 215 220

Lys Gly Asn Leu Thr Pro Leu Thr Gly Arg Asn Tyr Arg Gln Leu Leu
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Glu Arg Leu Gln Ala Arg Gln Ser Arg Leu Asp Glu Leu Arg Gly Gln
245 250 255

Asp Glu Gly Lys Ala Gln Glu Leu Glu Ala Lys Met Lys Trp Thr Asn
260 265 270

Leu Leu Tyr Lys Ala Glu Gly Val Lys Ile Arg Asp Asp Glu Arg Leu
275 280 285

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290 295 300

Arg Arg Trp Glu Lys Arg Thr Ala Gly Val Val Glu Lys Met Gln Gln
305 310 315 320

Arg Gln Asp Arg Arg Arg Gln Asn Leu Arg Arg Lys Lys Ala Ala Arg
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tgccacctta gtctggctgg ggaggcggac gatgaggagt g atg ggg cag gca tgc 176
Met Gly Gln Ala Cys
1 5

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ggc cac tcc atc ctc tgc agg agc cag cag tac ccg gca gcg tga ccg   224
Gly His Ser Ile Leu Cys Arg Ser Gln Gln Tyr Pro Ala Ala Arg Pro
                 10                  15                  20

gct gag ccg cgg ggc cag cag gtc ttc ctc aag ccg gac gag ccg ccg   272
Ala Glu Pro Arg Gly Gln Gln Val Phe Leu Lys Pro Asp Glu Pro Pro
             25                  30                  35

ccg ccg ccg cag cca tgc gcc gac agc ctg cag gac gcc ttg ctg agt   320
Pro Pro Pro Gln Pro Cys Ala Asp Ser Leu Gln Asp Ala Leu Leu Ser
         40                  45                  50

ctg ggc tct gtc atc gac att tca ggc ctg caa cgt gct gtc aag gag   368
Leu Gly Ser Val Ile Asp Ile Ser Gly Leu Gln Arg Ala Val Lys Glu
     55                  60                  65

gcc ctg tca gct gtg ctc ccc cga gtg gaa act gtc tac acc tac cta   416
Ala Leu Ser Ala Val Leu Pro Arg Val Glu Thr Val Tyr Thr Tyr Leu
 70                  75                  80                  85

ctg gat ggt gag tcc cag ctg gtg tgt gag gac ccc cca cat gag ctg   464
Leu Asp Gly Glu Ser Gln Leu Val Cys Glu Asp Pro Pro His Glu Leu
                 90                  95                 100

ccc cag gag ggg aaa gtc cgg gag gct atc atc tcc cag aag cgg ctg   512
Pro Gln Glu Gly Lys Val Arg Glu Ala Ile Ile Ser Gln Lys Arg Leu
            105                 110                 115

ggc tgc aat ggg ctg ggc ttc tca gac ctg cca ggg aag ccc ttg gcc   560
Gly Cys Asn Gly Leu Gly Phe Ser Asp Leu Pro Gly Lys Pro Leu Ala
        120                 125                 130

agg ctg gtg gct cca ctg gct cct gat acc caa gtg ctg gtc atg ccg   608
Arg Leu Val Ala Pro Leu Ala Pro Asp Thr Gln Val Leu Val Met Pro
    135                 140                 145

cta gcg gac aag gag gct ggg gcc gtg gca gct gtc atc ttg gtg cac   656
Leu Ala Asp Lys Glu Ala Gly Ala Val Ala Ala Val Ile Leu Val His
150                 155                 160                 165

tgt ggc cag ctg agt gat aat gag gaa tgg agc ctg cag gcg gtg gag   704
Cys Gly Gln Leu Ser Asp Asn Glu Glu Trp Ser Leu Gln Ala Val Glu
                170                 175                 180

aag cat acc ctg gtc gcc ctg cgg agg gtg cag gtc ctg cag cag cgc   752
Lys His Thr Leu Val Ala Leu Arg Arg Val Gln Val Leu Gln Gln Arg
            185                 190                 195

ggg ccc agg gag gct ccc cga gcc gtc cag aac ccc ccg gag ggg acg   800
Gly Pro Arg Glu Ala Pro Arg Ala Val Gln Asn Pro Pro Glu Gly Thr
        200                 205                 210

gcg gaa gac cag aag ggc ggg gcg gcg tac acc gac cgc gac cgc aag   848
Ala Glu Asp Gln Lys Gly Gly Ala Ala Tyr Thr Asp Arg Asp Arg Lys
    215                 220                 225
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atc ctc caa ctg tgc ggg gaa ctc tac gac ctg gat gcc tct tcc ctg   896
Ile Leu Gln Leu Cys Gly Glu Leu Tyr Asp Leu Asp Ala Ser Ser Leu
230                 235                 240                 245

cag ctc aaa gtg ctc caa tac ctg cag cag gag acc cgg gca tcc cgc   944
Gln Leu Lys Val Leu Gln Tyr Leu Gln Gln Glu Thr Arg Ala Ser Arg
                250                 255                 260

tgc tgc ctc ctg ctg gtg tcg gag gac aat ctc cag ctt tct tgc aag   992
Cys Cys Leu Leu Leu Val Ser Glu Asp Asn Leu Gln Leu Ser Cys Lys
            265                 270                 275

gtc atc gga gac aaa gtg ctc ggg gaa gag gtc agc ttt ccc ttg aca   1040
Val Ile Gly Asp Lys Val Leu Gly Glu Glu Val Ser Phe Pro Leu Thr
        280                 285                 290

gga tgc ctg ggc cag gtg gtg gaa gac aag aag tcc atc cag ctg aag   1088
Gly Cys Leu Gly Gln Val Val Glu Asp Lys Lys Ser Ile Gln Leu Lys
    295                 300                 305

gac ctc acc tcc gag gat gta caa cag ctg cag agc atg ttg ggc tgt   1136
Asp Leu Thr Ser Glu Asp Val Gln Gln Leu Gln Ser Met Leu Gly Cys
310                 315                 320                 325

gag ctg cag gcc atg ctc tgt gtc cct gtc atc agc cgg gcc act gac   1184
Glu Leu Gln Ala Met Leu Cys Val Pro Val Ile Ser Arg Ala Thr Asp
                330                 335                 340

cag gtg gtg gcc ttg gcc tgc gcc ttc aac aag cta gaa gga gac ttg   1232
Gln Val Val Ala Leu Ala Cys Ala Phe Asn Lys Leu Glu Gly Asp Leu
            345                 350                 355

ttc acc gac gag gac gag cat gtg atc cag cac tgc ttc cac tac acc   1280
Phe Thr Asp Glu Asp Glu His Val Ile Gln His Cys Phe His Tyr Thr
        360                 365                 370

agc acc gtg ctc acc agc acc ctg gcc ttc cag aag gaa cag aaa ctc   1328
Ser Thr Val Leu Thr Ser Thr Leu Ala Phe Gln Lys Glu Gln Lys Leu
    375                 380                 385

aag tgt gag tgc cag gct ctt ctc caa gtg gca aag aac ctc ttc acc   1376
Lys Cys Glu Cys Gln Ala Leu Leu Gln Val Ala Lys Asn Leu Phe Thr
390                 395                 400                 405

cac ctg gat gac gtc tct gtc ctg ctc cag gag atc atc acg gag gcc   1424
His Leu Asp Asp Val Ser Val Leu Leu Gln Glu Ile Ile Thr Glu Ala
                410                 415                 420

aga aac ctc agc aac gca gag atc tgc tct gtg ttc ctg ctg gat cag   1472
Arg Asn Leu Ser Asn Ala Glu Ile Cys Ser Val Phe Leu Leu Asp Gln
            425                 430                 435

aat gag ctg gtg gcc aag gtg ttc gac ggg ggc gtg gtg gat gat gag   1520
Asn Glu Leu Val Ala Lys Val Phe Asp Gly Gly Val Val Asp Asp Glu
        440                 445                 450
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agc tat gag atc cgc atc ccg gcc gat cag ggc atc gcg gga cac gtg   1568
Ser Tyr Glu Ile Arg Ile Pro Ala Asp Gln Gly Ile Ala Gly His Val
    455                 460                 465

gcg acc acg ggc cag atc ctg aac atc cct gac gca tat gcc cat ccg   1616
Ala Thr Thr Gly Gln Ile Leu Asn Ile Pro Asp Ala Tyr Ala His Pro
470                 475                 480                 485

ctt ttc tac cgc ggc gtg gac gac agc acc ggc ttc cgc acg cgc aac   1664
Leu Phe Tyr Arg Gly Val Asp Asp Ser Thr Gly Phe Arg Thr Arg Asn
                490                 495                 500

atc ctc tgc ttc ccc atc aag aac gag aac cag gag gtc atc ggt gtg   1712
Ile Leu Cys Phe Pro Ile Lys Asn Glu Asn Gln Glu Val Ile Gly Val
            505                 510                 515

gcc gag ctg gtg aac aag atc aat ggg cca tgg ttc agc aag ttc gac   1760
Ala Glu Leu Val Asn Lys Ile Asn Gly Pro Trp Phe Ser Lys Phe Asp
        520                 525                 530

gag gac ctg gcg acg gcc ttc tcc atc tac tgc ggc atc agc atc gcc   1808
Glu Asp Leu Ala Thr Ala Phe Ser Ile Tyr Cys Gly Ile Ser Ile Ala
    535                 540                 545

cat tct ctc cta tac aaa aaa gtg aat gag gct cag tat cgc agc cac   1856
His Ser Leu Leu Tyr Lys Lys Val Asn Glu Ala Gln Tyr Arg Ser His
550                 555                 560                 565

ctg gcc aat gag atg atg atg tac cac atg aag gtc tcc gac gat gag   1904
Leu Ala Asn Glu Met Met Met Tyr His Met Lys Val Ser Asp Asp Glu
                570                 575                 580

tat acc aaa ctt ctc cat gat ggg atc cag cct gtg gct gcc att gac   1952
Tyr Thr Lys Leu Leu His Asp Gly Ile Gln Pro Val Ala Ala Ile Asp
            585                 590                 595

tcc aat ttt gca agt ttc acc tat acc cct cgt tcc ctg ccc gag gat   2000
Ser Asn Phe Ala Ser Phe Thr Tyr Thr Pro Arg Ser Leu Pro Glu Asp
        600                 605                 610

gac acg tcc atg gcc atc ctg agc atg ctg cag gac atg aat ttc atc   2048
Asp Thr Ser Met Ala Ile Leu Ser Met Leu Gln Asp Met Asn Phe Ile
    615                 620                 625

aac aac tac aaa att gac tgc ccg acc ctg gcc cgg ttc tgt ttg atg   2096
Asn Asn Tyr Lys Ile Asp Cys Pro Thr Leu Ala Arg Phe Cys Leu Met
630                 635                 640                 645

gtg aag aag ggc tac cgg gat ccc ccc tac cac aac tgg atg cac gcc   2144
Val Lys Lys Gly Tyr Arg Asp Pro Pro Tyr His Asn Trp Met His Ala
                650                 655                 660

ttt tct gtc tcc cac ttc tgc tac ctg ctc tac aag aac ctg gag ctc   2192
Phe Ser Val Ser His Phe Cys Tyr Leu Leu Tyr Lys Asn Leu Glu Leu
            665                 670                 675
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acc aac tac ctc gag gac atc gag atc ttt gcc ttg ttt att tcc tgc   2240
Thr Asn Tyr Leu Glu Asp Ile Glu Ile Phe Ala Leu Phe Ile Ser Cys
        680                 685                 690

atg tgt cat gac ctg gac cac aga ggc aca aac aac tct ttc cag gtg   2288
Met Cys His Asp Leu Asp His Arg Gly Thr Asn Asn Ser Phe Gln Val
    695                 700                 705

gcc tcg aaa tct gtg ctg gct gcg ctc tac agc tct gag ggc tcc gtc   2336
Ala Ser Lys Ser Val Leu Ala Ala Leu Tyr Ser Ser Glu Gly Ser Val
710                 715                 720                 725

atg gag agg cac cac ttt gct cag gcc atc gcc atc ctc aac acc cac   2384
Met Glu Arg His His Phe Ala Gln Ala Ile Ala Ile Leu Asn Thr His
                730                 735                 740

ggc tgc aac atc ttt gat cat ttc tcc cgg aag gac tat cag cgc atg   2432
Gly Cys Asn Ile Phe Asp His Phe Ser Arg Lys Asp Tyr Gln Arg Met
            745                 750                 755

ctg gat ctg atg cgg gac atc atc ttg gcc aca gac ctg gcc cac cat   2480
Leu Asp Leu Met Arg Asp Ile Ile Leu Ala Thr Asp Leu Ala His His
        760                 765                 770

ctc cgc atc ttc aag gac ctc cag aag atg gct gag gtg ggc tac gac   2528
Leu Arg Ile Phe Lys Asp Leu Gln Lys Met Ala Glu Val Gly Tyr Asp
    775                 780                 785

cga aac aac aag cag cac cac aga ctt ctc ctc tgc ctc ctc atg acc   2576
Arg Asn Asn Lys Gln His His Arg Leu Leu Leu Cys Leu Leu Met Thr
790                 795                 800                 805

tcc tgt gac ctc tct gac cag acc aag ggc tgg aag act acg aga aag   2624
Ser Cys Asp Leu Ser Asp Gln Thr Lys Gly Trp Lys Thr Thr Arg Lys
                810                 815                 820

atc gcg gag ctg atc tac aaa gaa ttc ttc tcc cag gga gac ctg gag   2672
Ile Ala Glu Leu Ile Tyr Lys Glu Phe Phe Ser Gln Gly Asp Leu Glu
            825                 830                 835

aag gcc atg ggc aac agg ccg atg gag atg atg gac cgg gag aag gcc   2720
Lys Ala Met Gly Asn Arg Pro Met Glu Met Met Asp Arg Glu Lys Ala
        840                 845                 850

tat atc cct gag ctg caa atc agc ttc atg gag cac att gca atg ccc   2768
Tyr Ile Pro Glu Leu Gln Ile Ser Phe Met Glu His Ile Ala Met Pro
    855                 860                 865

atc tac aag ctg ttg cag gac ctg ttc ccc aaa gcg gca gag ctg tac   2816
Ile Tyr Lys Leu Leu Gln Asp Leu Phe Pro Lys Ala Ala Glu Leu Tyr
870                 875                 880                 885

gag cgc gtg gcc tcc aac cgt gag cac tgg acc aag gtg tcc cac aag   2864
Glu Arg Val Ala Ser Asn Arg Glu His Trp Thr Lys Val Ser His Lys
                890                 895                 900
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ttc acc atc cgc ggc ctc cca agt aac aac tcg ctg gac ttc ctg gat 2912
Phe Thr Ile Arg Gly Leu Pro Ser Asn Asn Ser Leu Asp Phe Leu Asp
905 910 915

gag gag tac gag gtg cct gat ctg gat ggc act agg gcc ccc atc aat 2960
Glu Glu Tyr Glu Val Pro Asp Leu Asp Gly Thr Arg Ala Pro Ile Asn
920 925 930

ggc tgc tgc agc ctt gat gct gag tga tcccctccag gacacttccc 3007
Gly Cys Cys Ser Leu Asp Ala Glu
935 940

tgcccaggcc acctcccaca gccctccact ggtctggcca gatgcactgg gaacagagcc 3067

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Pro Asp Glu Pro Pro Pro Pro Pro Gln Pro Cys Ala Asp Ser Leu Gln
        35                  40                  45

Asp Ala Leu Leu Ser Leu Gly Ser Val Ile Asp Ile Ser Gly Leu Gln
    50                  55                  60

Arg Ala Val Lys Glu Ala Leu Ser Ala Val Leu Pro Arg Val Glu Thr
65                  70                  75                  80

Val Tyr Thr Tyr Leu Leu Asp Gly Glu Ser Gln Leu Val Cys Glu Asp
                85                  90                  95

Pro Pro His Glu Leu Pro Gln Glu Gly Lys Val Arg Glu Ala Ile Ile
            100                 105                 110

Ser Gln Lys Arg Leu Gly Cys Asn Gly Leu Gly Phe Ser Asp Leu Pro
        115                 120                 125

Gly Lys Pro Leu Ala Arg Leu Val Ala Pro Leu Ala Pro Asp Thr Gln
    130                 135                 140

Val Leu Val Met Pro Leu Ala Asp Lys Glu Ala Gly Ala Val Ala Ala
145                 150                 155                 160

Val Ile Leu Val His Cys Gly Gln Leu Ser Asp Asn Glu Glu Trp Ser
                165                 170                 175

Leu Gln Ala Val Glu Lys His Thr Leu Val Ala Leu Arg Arg Val Gln
            180                 185                 190

Val Leu Gln Gln Arg Gly Pro Arg Glu Ala Pro Arg Ala Val Gln Asn
        195                 200                 205

Pro Pro Glu Gly Thr Ala Glu Asp Gln Lys Gly Gly Ala Ala Tyr Thr
    210                 215                 220

Asp Arg Asp Arg Lys Ile Leu Gln Leu Cys Gly Glu Leu Tyr Asp Leu
225                 230                 235                 240

Asp Ala Ser Ser Leu Gln Leu Lys Val Leu Gln Tyr Leu Gln Gln Glu
                245                 250                 255

Thr Arg Ala Ser Arg Cys Cys Leu Leu Leu Val Ser Glu Asp Asn Leu
            260                 265                 270
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Gln Leu Ser Cys Lys Val Ile Gly Asp Lys Val Leu Gly Glu Glu Val
        275                 280                 285

Ser Phe Pro Leu Thr Gly Cys Leu Gly Gln Val Val Glu Asp Lys Lys
    290                 295                 300

Ser Ile Gln Leu Lys Asp Leu Thr Ser Glu Asp Val Gln Gln Leu Gln
305                 310                 315                 320

Ser Met Leu Gly Cys Glu Leu Gln Ala Met Leu Cys Val Pro Val Ile
                325                 330                 335

Ser Arg Ala Thr Asp Gln Val Val Ala Leu Ala Cys Ala Phe Asn Lys
            340                 345                 350

Leu Glu Gly Asp Leu Phe Thr Asp Glu Asp Glu His Val Ile Gln His
        355                 360                 365

Cys Phe His Tyr Thr Ser Thr Val Leu Thr Ser Thr Leu Ala Phe Gln
    370                 375                 380

Lys Glu Gln Lys Leu Lys Cys Glu Cys Gln Ala Leu Leu Gln Val Ala
385                 390                 395                 400

Lys Asn Leu Phe Thr His Leu Asp Asp Val Ser Val Leu Leu Gln Glu
                405                 410                 415

Ile Ile Thr Glu Ala Arg Asn Leu Ser Asn Ala Glu Ile Cys Ser Val
            420                 425                 430

Phe Leu Leu Asp Gln Asn Glu Leu Val Ala Lys Val Phe Asp Gly Gly
        435                 440                 445

Val Val Asp Asp Glu Ser Tyr Glu Ile Arg Ile Pro Ala Asp Gln Gly
    450                 455                 460

Ile Ala Gly His Val Ala Thr Thr Gly Gln Ile Leu Asn Ile Pro Asp
465                 470                 475                 480

Ala Tyr Ala His Pro Leu Phe Tyr Arg Gly Val Asp Asp Ser Thr Gly
                485                 490                 495

Phe Arg Thr Arg Asn Ile Leu Cys Phe Pro Ile Lys Asn Glu Asn Gln
            500                 505                 510

Glu Val Ile Gly Val Ala Glu Leu Val Asn Lys Ile Asn Gly Pro Trp
        515                 520                 525

Phe Ser Lys Phe Asp Glu Asp Leu Ala Thr Ala Phe Ser Ile Tyr Cys
    530                 535                 540

Gly Ile Ser Ile Ala His Ser Leu Leu Tyr Lys Lys Val Asn Glu Ala
545                 550                 555                 560
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Gln Tyr Arg Ser His Leu Ala Asn Glu Met Met Met Tyr His Met Lys
                565                 570                 575

Val Ser Asp Asp Glu Tyr Thr Lys Leu Leu His Asp Gly Ile Gln Pro
            580                 585                 590

Val Ala Ala Ile Asp Ser Asn Phe Ala Ser Phe Thr Tyr Thr Pro Arg
        595                 600                 605

Ser Leu Pro Glu Asp Asp Thr Ser Met Ala Ile Leu Ser Met Leu Gln
    610                 615                 620

Asp Met Asn Phe Ile Asn Asn Tyr Lys Ile Asp Cys Pro Thr Leu Ala
625                 630                 635                 640

Arg Phe Cys Leu Met Val Lys Lys Gly Tyr Arg Asp Pro Pro Tyr His
                645                 650                 655

Asn Trp Met His Ala Phe Ser Val Ser His Phe Cys Tyr Leu Leu Tyr
            660                 665                 670

Lys Asn Leu Glu Leu Thr Asn Tyr Leu Glu Asp Ile Glu Ile Phe Ala
        675                 680                 685

Leu Phe Ile Ser Cys Met Cys His Asp Leu Asp His Arg Gly Thr Asn
    690                 695                 700

Asn Ser Phe Gln Val Ala Ser Lys Ser Val Leu Ala Ala Leu Tyr Ser
705                 710                 715                 720

Ser Glu Gly Ser Val Met Glu Arg His His Phe Ala Gln Ala Ile Ala
                725                 730                 735

Ile Leu Asn Thr His Gly Cys Asn Ile Phe Asp His Phe Ser Arg Lys
            740                 745                 750

Asp Tyr Gln Arg Met Leu Asp Leu Met Arg Asp Ile Ile Leu Ala Thr
        755                 760                 765

Asp Leu Ala His His Leu Arg Ile Phe Lys Asp Leu Gln Lys Met Ala
    770                 775                 780

Glu Val Gly Tyr Asp Arg Asn Asn Lys Gln His His Arg Leu Leu Leu
785                 790                 795                 800

Cys Leu Leu Met Thr Ser Cys Asp Leu Ser Asp Gln Thr Lys Gly Trp
                805                 810                 815

Lys Thr Thr Arg Lys Ile Ala Glu Leu Ile Tyr Lys Glu Phe Phe Ser
            820                 825                 830

Gln Gly Asp Leu Glu Lys Ala Met Gly Asn Arg Pro Met Glu Met Met
        835                 840                 845

Asp Arg Glu Lys Ala Tyr Ile Pro Glu Leu Gln Ile Ser Phe Met Glu
    850                 855                 860
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His Ile Ala Met Pro Ile Tyr Lys Leu Leu Gln Asp Leu Phe Pro Lys
865                 870                 875                 880

Ala Ala Glu Leu Tyr Glu Arg Val Ala Ser Asn Arg Glu His Trp Thr
                885                 890                 895

Lys Val Ser His Lys Phe Thr Ile Arg Gly Leu Pro Ser Asn Asn Ser
            900                 905                 910

Leu Asp Phe Leu Asp Glu Glu Tyr Glu Val Pro Asp Leu Asp Gly Thr
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Arg Ala Pro Ile Asn Gly Cys Cys Ser Leu Asp Ala Glu
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atg caa tgg cga gcg ctc gtc ctg ggg ctg gtg ctc ctc cgg ctt ggc   106
Met Gln Trp Arg Ala Leu Val Leu Gly Leu Val Leu Leu Arg Leu Gly
  1               5                  10                  15

ctc cat gga gta ttg tgg ctc gtc ttc ggg ctg ggg ccc agc atg ggc   154
Leu His Gly Val Leu Trp Leu Val Phe Gly Leu Gly Pro Ser Met Gly
            20                  25                  30

ttc tac cag cgc ttt ccg ctc agc ttc ggc ttc cag cgt ctg agg agc   202
Phe Tyr Gln Arg Phe Pro Leu Ser Phe Gly Phe Gln Arg Leu Arg Ser
        35                  40                  45

ccc gac ggc ccc gcg tcg ccc acc tcg ggg ccc gtg ggc cgg cct ggg   250
Pro Asp Gly Pro Ala Ser Pro Thr Ser Gly Pro Val Gly Arg Pro Gly
    50                  55                  60

ggg gta tcc ggg ccg tcg tgg ctg cag ccg ccg ggg acc ggg gca gcg   298
Gly Val Ser Gly Pro Ser Trp Leu Gln Pro Pro Gly Thr Gly Ala Ala
65                  70                  75                  80

cag agc ccg cgc aag gct ccg cgg cgt cct ggg ccg ggg atg tgc ggc   346
Gln Ser Pro Arg Lys Ala Pro Arg Arg Pro Gly Pro Gly Met Cys Gly
                85                  90                  95

cca gcc aac tgg ggc tac gtg ctg ggc ggc cgg ggc cgc ggc ccg gac   394
Pro Ala Asn Trp Gly Tyr Val Leu Gly Gly Arg Gly Arg Gly Pro Asp
            100                 105                 110
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gag tac gag aag cgc tac agc ggc gcc ttc cct ccg cag ctg cgt gcc   442
Glu Tyr Glu Lys Arg Tyr Ser Gly Ala Phe Pro Pro Gln Leu Arg Ala
        115                 120                 125

cag atg cgc gac ctg gca cgg ggc atg ttc gtc ttt ggc tac gac aac   490
Gln Met Arg Asp Leu Ala Arg Gly Met Phe Val Phe Gly Tyr Asp Asn
    130                 135                 140

tac atg gct cac gcc ttc ccc cag gac gag ctc aac ccc atc cac tgc   538
Tyr Met Ala His Ala Phe Pro Gln Asp Glu Leu Asn Pro Ile His Cys
145                 150                 155                 160

cgc ggc cgt ggg ccc gac cgc ggg gac cct tca aat ctg aac atc aat   586
Arg Gly Arg Gly Pro Asp Arg Gly Asp Pro Ser Asn Leu Asn Ile Asn
                165                 170                 175

gat gta cta ggg aac tac tca ttg act ctt gtt gat gca ttg gat aca   634
Asp Val Leu Gly Asn Tyr Ser Leu Thr Leu Val Asp Ala Leu Asp Thr
            180                 185                 190

ctt gca ata atg gga aat tca tcc gag ttc cag aaa gca gtc aag tta   682
Leu Ala Ile Met Gly Asn Ser Ser Glu Phe Gln Lys Ala Val Lys Leu
        195                 200                 205

gtg atc aac aca gtt tca ttt gac aaa gat tcc acc gtc caa gtc ttt   730
Val Ile Asn Thr Val Ser Phe Asp Lys Asp Ser Thr Val Gln Val Phe
    210                 215                 220

gag gcc acg ata agg gtc ctg gga agc ctc ctt tct gct cac aga ata   778
Glu Ala Thr Ile Arg Val Leu Gly Ser Leu Leu Ser Ala His Arg Ile
225                 230                 235                 240

ata act gac tcc aag cag ccc ttt ggt gac atg aca att aag gac tat   826
Ile Thr Asp Ser Lys Gln Pro Phe Gly Asp Met Thr Ile Lys Asp Tyr
                245                 250                 255

gat aat gag ttg tta tac atg gcc cat gac ctg gcg gtg cgg ctc ctc   874
Asp Asn Glu Leu Leu Tyr Met Ala His Asp Leu Ala Val Arg Leu Leu
            260                 265                 270

cct gct ttt gaa aac acc aag aca ggg att cca tat cct cgg gtg aat   922
Pro Ala Phe Glu Asn Thr Lys Thr Gly Ile Pro Tyr Pro Arg Val Asn
        275                 280                 285

cta aag aca gga gtt cct cct gac acc aat aat gag aca tgc aca gcg   970
Leu Lys Thr Gly Val Pro Pro Asp Thr Asn Asn Glu Thr Cys Thr Ala
    290                 295                 300

gga gcc ggt tcc ctc ctg gtg gaa ttt ggg att ctg agt cga ctc ctg   1018
Gly Ala Gly Ser Leu Leu Val Glu Phe Gly Ile Leu Ser Arg Leu Leu
305                 310                 315                 320

ggg gac tcc aca ttt gag tgg gtg gcc aga cga gca gtg aaa gcc ctt   1066
Gly Asp Ser Thr Phe Glu Trp Val Ala Arg Arg Ala Val Lys Ala Leu
                325                 330                 335
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tgg aac ctc cgg agc aat gat aca gga tta cta ggc aat gtc gtg aac   1114
Trp Asn Leu Arg Ser Asn Asp Thr Gly Leu Leu Gly Asn Val Val Asn
            340                 345                 350

att cag acg ggc cac tgg gtt gga aag cag agt ggc ctg ggt gcc ggg   1162
Ile Gln Thr Gly His Trp Val Gly Lys Gln Ser Gly Leu Gly Ala Gly
        355                 360                 365

ctg gac tcc ttc tat gaa tac ctc ttg aaa tct tac att ctc ttt gga   1210
Leu Asp Ser Phe Tyr Glu Tyr Leu Leu Lys Ser Tyr Ile Leu Phe Gly
    370                 375                 380

gaa aaa gaa gac cta gaa atg ttt aat gct gca tat cag agt att cag   1258
Glu Lys Glu Asp Leu Glu Met Phe Asn Ala Ala Tyr Gln Ser Ile Gln
385                 390                 395                 400

aac tac tta aga aga ggg cgg gaa gcc tgc aat gaa gga gaa gga gac   1306
Asn Tyr Leu Arg Arg Gly Arg Glu Ala Cys Asn Glu Gly Glu Gly Asp
                405                 410                 415

cct cca ctc tat gtc aac gtg aac atg ttc agt ggg cag ctg atg aac   1354
Pro Pro Leu Tyr Val Asn Val Asn Met Phe Ser Gly Gln Leu Met Asn
            420                 425                 430

acc tgg att gac tct ctg cag gcc ttt ttc cct gga ctg cag gtg ctg   1402
Thr Trp Ile Asp Ser Leu Gln Ala Phe Phe Pro Gly Leu Gln Val Leu
        435                 440                 445

ata gga gat gtg gaa gat gcc atc tgc ctt cat gcc ttc tac tat gcc   1450
Ile Gly Asp Val Glu Asp Ala Ile Cys Leu His Ala Phe Tyr Tyr Ala
    450                 455                 460

ata tgg aaa cga tat ggt gcc ctc cct gag aga tat aac tgg cag ctg   1498
Ile Trp Lys Arg Tyr Gly Ala Leu Pro Glu Arg Tyr Asn Trp Gln Leu
465                 470                 475                 480

cag gcc cct gac gtt ctc ttc tac cca ctg aga cca gag tta gtg gaa   1546
Gln Ala Pro Asp Val Leu Phe Tyr Pro Leu Arg Pro Glu Leu Val Glu
                485                 490                 495

tcc aca tat ctc ctc tac cag gca acc aag aat ccc ttc tac ctc cat   1594
Ser Thr Tyr Leu Leu Tyr Gln Ala Thr Lys Asn Pro Phe Tyr Leu His
            500                 505                 510

gta gga atg gat att ctg cag agt ctg gaa aag tac aca aaa gtc aag   1642
Val Gly Met Asp Ile Leu Gln Ser Leu Glu Lys Tyr Thr Lys Val Lys
        515                 520                 525

tgt ggg tac gcc acg ctg cat cac gtc att gac aag tcc aca gaa gac   1690
Cys Gly Tyr Ala Thr Leu His His Val Ile Asp Lys Ser Thr Glu Asp
    530                 535                 540

cgg atg gag agc ttc ttt ctc agt gag acc tgt aaa tat ttg tat ctg   1738
Arg Met Glu Ser Phe Phe Leu Ser Glu Thr Cys Lys Tyr Leu Tyr Leu
545                 550                 555                 560
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ctg ttt gat gaa gac aat cca gta cac aag tct gga acc aga tac atg   1786
Leu Phe Asp Glu Asp Asn Pro Val His Lys Ser Gly Thr Arg Tyr Met
                565                 570                 575

ttc aca aca gag gga cac att gta tct gtg gat gag cat ctt cgg gaa   1834
Phe Thr Thr Glu Gly His Ile Val Ser Val Asp Glu His Leu Arg Glu
            580                 585                 590

ttg cca tgg aag gaa ttc ttc tct gaa gag gga ggg cag gac caa ggg   1882
Leu Pro Trp Lys Glu Phe Phe Ser Glu Glu Gly Gly Gln Asp Gln Gly
        595                 600                 605

gga aag tct gtg cac agg ccg aaa cct cat gag tta aaa gtc atc aac   1930
Gly Lys Ser Val His Arg Pro Lys Pro His Glu Leu Lys Val Ile Asn
    610                 615                 620

tcc agc tcc aac tgc aat cgt gta cct gat gag agg agg tac tcc ctg   1978
Ser Ser Ser Asn Cys Asn Arg Val Pro Asp Glu Arg Arg Tyr Ser Leu
625                 630                 635                 640

ccc tta aag agc atc tac atg cga cag att gac cag atg gtt ggt ttg   2026
Pro Leu Lys Ser Ile Tyr Met Arg Gln Ile Asp Gln Met Val Gly Leu
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            20                  25                  30

Phe Tyr Gln Arg Phe Pro Leu Ser Phe Gly Phe Gln Arg Leu Arg Ser
        35                  40                  45

Pro Asp Gly Pro Ala Ser Pro Thr Ser Gly Pro Val Gly Arg Pro Gly
    50                  55                  60

Gly Val Ser Gly Pro Ser Trp Leu Gln Pro Pro Gly Thr Gly Ala Ala
65                  70                  75                  80

Gln Ser Pro Arg Lys Ala Pro Arg Arg Pro Gly Pro Gly Met Cys Gly
                85                  90                  95

Pro Ala Asn Trp Gly Tyr Val Leu Gly Gly Arg Gly Arg Gly Pro Asp
            100                 105                 110

Glu Tyr Glu Lys Arg Tyr Ser Gly Ala Phe Pro Pro Gln Leu Arg Ala
        115                 120                 125

Gln Met Arg Asp Leu Ala Arg Gly Met Phe Val Phe Gly Tyr Asp Asn
    130                 135                 140

Tyr Met Ala His Ala Phe Pro Gln Asp Glu Leu Asn Pro Ile His Cys
145                 150                 155                 160

Arg Gly Arg Gly Pro Asp Arg Gly Asp Pro Ser Asn Leu Asn Ile Asn
                165                 170                 175

Asp Val Leu Gly Asn Tyr Ser Leu Thr Leu Val Asp Ala Leu Asp Thr
            180                 185                 190

Leu Ala Ile Met Gly Asn Ser Ser Glu Phe Gln Lys Ala Val Lys Leu
        195                 200                 205

Val Ile Asn Thr Val Ser Phe Asp Lys Asp Ser Thr Val Gln Val Phe
    210                 215                 220

Glu Ala Thr Ile Arg Val Leu Gly Ser Leu Leu Ser Ala His Arg Ile
225                 230                 235                 240

Ile Thr Asp Ser Lys Gln Pro Phe Gly Asp Met Thr Ile Lys Asp Tyr
                245                 250                 255

Asp Asn Glu Leu Leu Tyr Met Ala His Asp Leu Ala Val Arg Leu Leu
            260                 265                 270

Pro Ala Phe Glu Asn Thr Lys Thr Gly Ile Pro Tyr Pro Arg Val Asn
        275                 280                 285
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Leu Lys Thr Gly Val Pro Pro Asp Thr Asn Asn Glu Thr Cys Thr Ala
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Gly Ala Gly Ser Leu Leu Val Glu Phe Gly Ile Leu Ser Arg Leu Leu
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Gly Asp Ser Thr Phe Glu Trp Val Ala Arg Arg Ala Val Lys Ala Leu
                325                 330                 335

Trp Asn Leu Arg Ser Asn Asp Thr Gly Leu Leu Gly Asn Val Val Asn
            340                 345                 350

Ile Gln Thr Gly His Trp Val Gly Lys Gln Ser Gly Leu Gly Ala Gly
        355                 360                 365

Leu Asp Ser Phe Tyr Glu Tyr Leu Leu Lys Ser Tyr Ile Leu Phe Gly
    370                 375                 380

Glu Lys Glu Asp Leu Glu Met Phe Asn Ala Ala Tyr Gln Ser Ile Gln
385                 390                 395                 400

Asn Tyr Leu Arg Arg Gly Arg Glu Ala Cys Asn Glu Gly Glu Gly Asp
                405                 410                 415

Pro Pro Leu Tyr Val Asn Val Asn Met Phe Ser Gly Gln Leu Met Asn
            420                 425                 430

Thr Trp Ile Asp Ser Leu Gln Ala Phe Phe Pro Gly Leu Gln Val Leu
        435                 440                 445

Ile Gly Asp Val Glu Asp Ala Ile Cys Leu His Ala Phe Tyr Tyr Ala
    450                 455                 460

Ile Trp Lys Arg Tyr Gly Ala Leu Pro Glu Arg Tyr Asn Trp Gln Leu
465                 470                 475                 480

Gln Ala Pro Asp Val Leu Phe Tyr Pro Leu Arg Pro Glu Leu Val Glu
                485                 490                 495

Ser Thr Tyr Leu Leu Tyr Gln Ala Thr Lys Asn Pro Phe Tyr Leu His
            500                 505                 510

Val Gly Met Asp Ile Leu Gln Ser Leu Glu Lys Tyr Thr Lys Val Lys
        515                 520                 525

Cys Gly Tyr Ala Thr Leu His His Val Ile Asp Lys Ser Thr Glu Asp
    530                 535                 540

Arg Met Glu Ser Phe Phe Leu Ser Glu Thr Cys Lys Tyr Leu Tyr Leu
545                 550                 555                 560

Leu Phe Asp Glu Asp Asn Pro Val His Lys Ser Gly Thr Arg Tyr Met
                565                 570                 575

Phe Thr Thr Glu Gly His Ile Val Ser Val Asp Glu His Leu Arg Glu
            580                 585                 590
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Leu Pro Trp Lys Glu Phe Phe Ser Glu Glu Gly Gly Gln Asp Gln Gly
595 600 605

Gly Lys Ser Val His Arg Pro Lys Pro His Glu Leu Lys Val Ile Asn
610 615 620

Ser Ser Ser Asn Cys Asn Arg Val Pro Asp Glu Arg Arg Tyr Ser Leu
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Pro Leu Lys Ser Ile Tyr Met Arg Gln Ile Asp Gln Met Val Gly Leu
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Met Gly Asp Thr Val Val Glu Pro Ala Pro Leu Lys Pro Thr
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Ser Val Ile Thr Glu Gly Val Gly Glu Leu Ser Val Ile Asp Pro Glu
35 40 45

gtg gcc cag aag gcc tgc cag gag gtg ttg gag aaa gtc aag ctt ttg 614
Val Ala Gln Lys Ala Cys Gln Glu Val Leu Glu Lys Val Lys Leu Leu
50 55 60

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cat gga ggc gtg gca gtc tct agc aga ggc acc cca ctg gag ttg gtc   662
His Gly Gly Val Ala Val Ser Ser Arg Gly Thr Pro Leu Glu Leu Val
        65                  70                  75

aat ggg gat ggt gtg gac agt gag atc cgt tgc cta gat gat cca cct   710
Asn Gly Asp Gly Val Asp Ser Glu Ile Arg Cys Leu Asp Asp Pro Pro
    80                  85                  90

gcc cag atc agg gag gag gaa gat gag atg ggg gcc gct gtg gcc tca   758
Ala Gln Ile Arg Glu Glu Glu Asp Glu Met Gly Ala Ala Val Ala Ser
 95                 100                 105                 110

ggc aca gcc aaa gga gca aga aga cgg cgg cag aac aac tca gct aaa   806
Gly Thr Ala Lys Gly Ala Arg Arg Arg Arg Gln Asn Asn Ser Ala Lys
                115                 120                 125

cag tct tgg ctg ctg agg ctg ttt gag tca aaa ctg ttt gac atc tcc   854
Gln Ser Trp Leu Leu Arg Leu Phe Glu Ser Lys Leu Phe Asp Ile Ser
            130                 135                 140

atg gcc att tca tac ctg tat aac tcc aag gag cct gga gta caa gcc   902
Met Ala Ile Ser Tyr Leu Tyr Asn Ser Lys Glu Pro Gly Val Gln Ala
        145                 150                 155

tac att ggc aac cgg ctc ttc tgc ttt cgc aac gag gac gtg gac ttc   950
Tyr Ile Gly Asn Arg Leu Phe Cys Phe Arg Asn Glu Asp Val Asp Phe
    160                 165                 170

tat ctg ccc cag ttg ctt aac atg tac atc cac atg gat gag gac gtg   998
Tyr Leu Pro Gln Leu Leu Asn Met Tyr Ile His Met Asp Glu Asp Val
175                 180                 185                 190

ggt gat gcc att aag ccc tac ata gtc cac cgt tgc cgc cag agc att   1046
Gly Asp Ala Ile Lys Pro Tyr Ile Val His Arg Cys Arg Gln Ser Ile
                195                 200                 205

aac ttt tcc ctc cag tgt gcc ctg ttg ctt ggg gcc tat tct tca gac   1094
Asn Phe Ser Leu Gln Cys Ala Leu Leu Leu Gly Ala Tyr Ser Ser Asp
            210                 215                 220

atg cac att tcc act caa cga cac tcc cgt ggg acc aag cta cgg aag   1142
Met His Ile Ser Thr Gln Arg His Ser Arg Gly Thr Lys Leu Arg Lys
        225                 230                 235

ctg atc ctc tca gat gag cta aag cca gct cac agg aag agg gag ctg   1190
Leu Ile Leu Ser Asp Glu Leu Lys Pro Ala His Arg Lys Arg Glu Leu
    240                 245                 250

ccc tcc ttg agc ccg gcc cct gat aca ggg ctg tct ccc tcc aaa agg   1238
Pro Ser Leu Ser Pro Ala Pro Asp Thr Gly Leu Ser Pro Ser Lys Arg
255                 260                 265                 270

act cac cag cgc tct aag tca gat gcc act gcc agc ata agt ctc agc   1286
Thr His Gln Arg Ser Lys Ser Asp Ala Thr Ala Ser Ile Ser Leu Ser
                275                 280                 285
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agc aac ctg aaa cga aca gcc agc aac cct aaa gtg gag aat gag gat   1334
Ser Asn Leu Lys Arg Thr Ala Ser Asn Pro Lys Val Glu Asn Glu Asp
            290                 295                 300

gag gag ctc tcc tcc agc acc gag agt att gat aat tca ttc agt tcc   1382
Glu Glu Leu Ser Ser Ser Thr Glu Ser Ile Asp Asn Ser Phe Ser Ser
        305                 310                 315

cct gtt cga ctg gct cct gag aga gaa ttc atc aag tcc ctg atg gcg   1430
Pro Val Arg Leu Ala Pro Glu Arg Glu Phe Ile Lys Ser Leu Met Ala
    320                 325                 330

atc ggc aag cgg ctg gcc acg ctc ccc acc aaa gag cag aaa aca cag   1478
Ile Gly Lys Arg Leu Ala Thr Leu Pro Thr Lys Glu Gln Lys Thr Gln
335                 340                 345                 350

agg ctg atc tca gag ctc tcc ctg ctc aac cat aag ctc cct gcc cga   1526
Arg Leu Ile Ser Glu Leu Ser Leu Leu Asn His Lys Leu Pro Ala Arg
                355                 360                 365

gtc tgg ctg ccc act gct ggc ttt gac cac cac gtg gtc cgt gta ccc   1574
Val Trp Leu Pro Thr Ala Gly Phe Asp His His Val Val Arg Val Pro
            370                 375                 380

cac aca cag gct gtt gtc ctc aac tcc aag gac aag gct ccc tac ctg   1622
His Thr Gln Ala Val Val Leu Asn Ser Lys Asp Lys Ala Pro Tyr Leu
        385                 390                 395

att tat gtg gaa gtc ctt gaa tgt gaa aac ttt gac acc acc agt gtc   1670
Ile Tyr Val Glu Val Leu Glu Cys Glu Asn Phe Asp Thr Thr Ser Val
    400                 405                 410

cct gcc cgg atc ccc gag aac cga att cgg agt acg agg tcc gta gaa   1718
Pro Ala Arg Ile Pro Glu Asn Arg Ile Arg Ser Thr Arg Ser Val Glu
415                 420                 425                 430

aac ttg ccc gaa tgt ggt att acc cat gag cag cga gct ggc agc ttc   1766
Asn Leu Pro Glu Cys Gly Ile Thr His Glu Gln Arg Ala Gly Ser Phe
                435                 440                 445

agc act gtg ccc aac tat gac aac gat gat gag gcc tgg tcg gtg gat   1814
Ser Thr Val Pro Asn Tyr Asp Asn Asp Asp Glu Ala Trp Ser Val Asp
            450                 455                 460

gac ata ggc gag ctg caa gtg gag ctc ccc gaa gtg cat acc aac agc   1862
Asp Ile Gly Glu Leu Gln Val Glu Leu Pro Glu Val His Thr Asn Ser
        465                 470                 475

tgt gac aac atc tcc cag ttc tct gtg gac agc atc acc agc cag gag   1910
Cys Asp Asn Ile Ser Gln Phe Ser Val Asp Ser Ile Thr Ser Gln Glu
    480                 485                 490

agc aag gag cct gtg ttc att gca gca ggg gac atc cgc cgg cgc ctt   1958
Ser Lys Glu Pro Val Phe Ile Ala Ala Gly Asp Ile Arg Arg Arg Leu
495                 500                 505                 510
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tcg gaa cag ctg gct cat acc ccg aca gcc ttc aaa cga gac cca gaa   2006
Ser Glu Gln Leu Ala His Thr Pro Thr Ala Phe Lys Arg Asp Pro Glu
                515                 520                 525

gat cct tct gca gtt gct ctc aaa gag ccc tgg cag gag aaa gta cgg   2054
Asp Pro Ser Ala Val Ala Leu Lys Glu Pro Trp Gln Glu Lys Val Arg
            530                 535                 540

cgg atc aga gag ggc tcc ccc tac ggc cat ctc ccc aat tgg cgg ctc   2102
Arg Ile Arg Glu Gly Ser Pro Tyr Gly His Leu Pro Asn Trp Arg Leu
        545                 550                 555

ctg tca gtc att gtc aag tgt ggg gat gac ctt cgg caa gag ctt ctg   2150
Leu Ser Val Ile Val Lys Cys Gly Asp Asp Leu Arg Gln Glu Leu Leu
    560                 565                 570

gcc ttt cag gtg ttg aag caa ctg cag tcc att tgg gaa cag gag cga   2198
Ala Phe Gln Val Leu Lys Gln Leu Gln Ser Ile Trp Glu Gln Glu Arg
575                 580                 585                 590

gtg ccc ctt tgg atc aag cca tac aag att ctt gtg att tcg gct gat   2246
Val Pro Leu Trp Ile Lys Pro Tyr Lys Ile Leu Val Ile Ser Ala Asp
                595                 600                 605

agt ggc atg att gaa cca gtg gtc aat gct gtg tcc atc cat cag gtg   2294
Ser Gly Met Ile Glu Pro Val Val Asn Ala Val Ser Ile His Gln Val
            610                 615                 620

aag aaa cag tca cag ctc tcc ttg ctc gat tac ttc cta cag gag cac   2342
Lys Lys Gln Ser Gln Leu Ser Leu Leu Asp Tyr Phe Leu Gln Glu His
        625                 630                 635

ggc agt tac acc act gag gca ttc ctc agt gca cag cgc aat ttt gtg   2390
Gly Ser Tyr Thr Thr Glu Ala Phe Leu Ser Ala Gln Arg Asn Phe Val
    640                 645                 650

caa agt tgt gct ggg tac tgc ttg gtc tgc tac ctg ctg caa gtc aag   2438
Gln Ser Cys Ala Gly Tyr Cys Leu Val Cys Tyr Leu Leu Gln Val Lys
655                 660                 665                 670

gac aga cac aat ggg aat atc ctt ttg gac gca gaa ggc cac atc atc   2486
Asp Arg His Asn Gly Asn Ile Leu Leu Asp Ala Glu Gly His Ile Ile
                675                 680                 685

cac atc gac ttt ggc ttc atc ctc tcc agc tca ccc cga aat ctg ggc   2534
His Ile Asp Phe Gly Phe Ile Leu Ser Ser Ser Pro Arg Asn Leu Gly
            690                 695                 700

ttt gag acg tca gcc ttt aag ctg acc aca gag ttt gtg gat gtg atg   2582
Phe Glu Thr Ser Ala Phe Lys Leu Thr Thr Glu Phe Val Asp Val Met
        705                 710                 715

ggc ggc ctg gat ggc gac atg ttc aac tac tat aag atg ctg atg ctg   2630
Gly Gly Leu Asp Gly Asp Met Phe Asn Tyr Tyr Lys Met Leu Met Leu
    720                 725                 730
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caa ggg ctg att gcc gct cgg aaa cac atg gac aag gtg gtg cag atc 2678
Gln Gly Leu Ile Ala Ala Arg Lys His Met Asp Lys Val Val Gln Ile
735 740 745 750

gtg gag atc atg cag caa ggt tct cag ctt cct tgc ttc cat ggc tcc 2726
Val Glu Ile Met Gln Gln Gly Ser Gln Leu Pro Cys Phe His Gly Ser
755 760 765

agc acc att cga aac ctc aaa gag agg ttc cac atg agc atg act gag 2774
Ser Thr Ile Arg Asn Leu Lys Glu Arg Phe His Met Ser Met Thr Glu
770 775 780

gag cag ctg cag ctg ctg gtg gag cag atg gtg gat ggc agt atg cgg 2822
Glu Gln Leu Gln Leu Leu Val Glu Gln Met Val Asp Gly Ser Met Arg
785 790 795

tct atc acc acc aaa ctc tat gac ggc ttc cag tac ctc acc aac ggc 2870
Ser Ile Thr Thr Lys Leu Tyr Asp Gly Phe Gln Tyr Leu Thr Asn Gly
800 805 810

atc atg tga cacgctcctc agcccaggag tggtgggggg tccagggcac 2919
Ile Met
815

cctccctaga gggcccttgt ctgagaaacc ccaaaccagg aaaccccacc tacccaacca 2979

tccacccaag ggaaatggaa ggcaagaaac acgaaggatc atgtggtaac tgcgagagct 3039

tgctgagggg tgggagagcc agctgtgggg tccagacttg ttggggcttc cctgcccctc 3099

ctggtctgtg tcagtattac caccagactg actccaggac tcactgccct ccagaaaaca 3159

gaggtgacaa atgtgaggga cactggggcc tttcttctcc ttgtaggggt ctctcagagg 3219

ttctttccac aggccatcct cttattccgt tctggggccc aggaagtggg gaagagtagg 3279

ttctcggtac ttaggacttg atcctgtggt tgccactggc catgctgctg cccagctcta 3339

cccctcccag ggacctaccc ctcccaggga ccgacccctg gcccaagctc cccttgctgg 3399

cgggcgctgc gtgggccctg cacttgctga ggttccccat catgggcaag gcaagggaat 3459

tcccacagcc ctccagtgta ctgagggtac tggcctagcc atgtggaatt ccctaccctg 3519

actccttccc caaacccagg gaaaagagct ctcaattttt tatttttaat ttttgtttga 3579

aataaagtcc ttagttagcc 3599

<210> 22
<211> 817
<212> PRT
<213> Homo sapiens

<400> 22

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Met Gly Asp Thr Val Val Glu Pro Ala Pro Leu Lys Pro Thr Ser Glu
 1               5                  10                  15

Pro Thr Ser Gly Pro Pro Gly Asn Asn Gly Gly Ser Leu Leu Ser Val
            20                  25                  30

Ile Thr Glu Gly Val Gly Glu Leu Ser Val Ile Asp Pro Glu Val Ala
        35                  40                  45

Gln Lys Ala Cys Gln Glu Val Leu Glu Lys Val Lys Leu Leu His Gly
    50                  55                  60

Gly Val Ala Val Ser Ser Arg Gly Thr Pro Leu Glu Leu Val Asn Gly
65                  70                  75                  80

Asp Gly Val Asp Ser Glu Ile Arg Cys Leu Asp Asp Pro Pro Ala Gln
                85                  90                  95

Ile Arg Glu Glu Glu Asp Glu Met Gly Ala Ala Val Ala Ser Gly Thr
            100                 105                 110

Ala Lys Gly Ala Arg Arg Arg Arg Gln Asn Asn Ser Ala Lys Gln Ser
        115                 120                 125

Trp Leu Leu Arg Leu Phe Glu Ser Lys Leu Phe Asp Ile Ser Met Ala
    130                 135                 140

Ile Ser Tyr Leu Tyr Asn Ser Lys Glu Pro Gly Val Gln Ala Tyr Ile
145                 150                 155                 160

Gly Asn Arg Leu Phe Cys Phe Arg Asn Glu Asp Val Asp Phe Tyr Leu
                165                 170                 175

Pro Gln Leu Leu Asn Met Tyr Ile His Met Asp Glu Asp Val Gly Asp
            180                 185                 190

Ala Ile Lys Pro Tyr Ile Val His Arg Cys Arg Gln Ser Ile Asn Phe
        195                 200                 205

Ser Leu Gln Cys Ala Leu Leu Leu Gly Ala Tyr Ser Ser Asp Met His
    210                 215                 220

Ile Ser Thr Gln Arg His Ser Arg Gly Thr Lys Leu Arg Lys Leu Ile
225                 230                 235                 240

Leu Ser Asp Glu Leu Lys Pro Ala His Arg Lys Arg Glu Leu Pro Ser
                245                 250                 255

Leu Ser Pro Ala Pro Asp Thr Gly Leu Ser Pro Ser Lys Arg Thr His
            260                 265                 270

Gln Arg Ser Lys Ser Asp Ala Thr Ala Ser Ile Ser Leu Ser Ser Asn
        275                 280                 285

Leu Lys Arg Thr Ala Ser Asn Pro Lys Val Glu Asn Glu Asp Glu Glu
    290                 295                 300
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Leu Ser Ser Ser Thr Glu Ser Ile Asp Asn Ser Phe Ser Ser Pro Val
305                 310                 315                 320

Arg Leu Ala Pro Glu Arg Glu Phe Ile Lys Ser Leu Met Ala Ile Gly
                325                 330                 335

Lys Arg Leu Ala Thr Leu Pro Thr Lys Glu Gln Lys Thr Gln Arg Leu
            340                 345                 350

Ile Ser Glu Leu Ser Leu Leu Asn His Lys Leu Pro Ala Arg Val Trp
        355                 360                 365

Leu Pro Thr Ala Gly Phe Asp His His Val Val Arg Val Pro His Thr
    370                 375                 380

Gln Ala Val Val Leu Asn Ser Lys Asp Lys Ala Pro Tyr Leu Ile Tyr
385                 390                 395                 400

Val Glu Val Leu Glu Cys Glu Asn Phe Asp Thr Thr Ser Val Pro Ala
                405                 410                 415

Arg Ile Pro Glu Asn Arg Ile Arg Ser Thr Arg Ser Val Glu Asn Leu
            420                 425                 430

Pro Glu Cys Gly Ile Thr His Glu Gln Arg Ala Gly Ser Phe Ser Thr
        435                 440                 445

Val Pro Asn Tyr Asp Asn Asp Asp Glu Ala Trp Ser Val Asp Asp Ile
    450                 455                 460

Gly Glu Leu Gln Val Glu Leu Pro Glu Val His Thr Asn Ser Cys Asp
465                 470                 475                 480

Asn Ile Ser Gln Phe Ser Val Asp Ser Ile Thr Ser Gln Glu Ser Lys
                485                 490                 495

Glu Pro Val Phe Ile Ala Ala Gly Asp Ile Arg Arg Arg Leu Ser Glu
            500                 505                 510

Gln Leu Ala His Thr Pro Thr Ala Phe Lys Arg Asp Pro Glu Asp Pro
        515                 520                 525

Ser Ala Val Ala Leu Lys Glu Pro Trp Gln Glu Lys Val Arg Arg Ile
    530                 535                 540

Arg Glu Gly Ser Pro Tyr Gly His Leu Pro Asn Trp Arg Leu Leu Ser
545                 550                 555                 560

Val Ile Val Lys Cys Gly Asp Asp Leu Arg Gln Glu Leu Leu Ala Phe
                565                 570                 575

Gln Val Leu Lys Gln Leu Gln Ser Ile Trp Glu Gln Glu Arg Val Pro
            580                 585                 590
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Leu Trp Ile Lys Pro Tyr Lys Ile Leu Val Ile Ser Ala Asp Ser Gly
        595                 600                 605

Met Ile Glu Pro Val Val Asn Ala Val Ser Ile His Gln Val Lys Lys
    610                 615                 620

Gln Ser Gln Leu Ser Leu Leu Asp Tyr Phe Leu Gln Glu His Gly Ser
625                 630                 635                 640

Tyr Thr Thr Glu Ala Phe Leu Ser Ala Gln Arg Asn Phe Val Gln Ser
                645                 650                 655

Cys Ala Gly Tyr Cys Leu Val Cys Tyr Leu Leu Gln Val Lys Asp Arg
            660                 665                 670

His Asn Gly Asn Ile Leu Leu Asp Ala Glu Gly His Ile Ile His Ile
        675                 680                 685

Asp Phe Gly Phe Ile Leu Ser Ser Ser Pro Arg Asn Leu Gly Phe Glu
    690                 695                 700

Thr Ser Ala Phe Lys Leu Thr Thr Glu Phe Val Asp Val Met Gly Gly
705                 710                 715                 720

Leu Asp Gly Asp Met Phe Asn Tyr Tyr Lys Met Leu Met Leu Gln Gly
                725                 730                 735

Leu Ile Ala Ala Arg Lys His Met Asp Lys Val Val Gln Ile Val Glu
            740                 745                 750

Ile Met Gln Gln Gly Ser Gln Leu Pro Cys Phe His Gly Ser Ser Thr
        755                 760                 765

Ile Arg Asn Leu Lys Glu Arg Phe His Met Ser Met Thr Glu Glu Gln
    770                 775                 780

Leu Gln Leu Leu Val Glu Gln Met Val Asp Gly Ser Met Arg Ser Ile
785                 790                 795                 800

Thr Thr Lys Leu Tyr Asp Gly Phe Gln Tyr Leu Thr Asn Gly Ile Met
                805                 810                 815
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<210> 23
<211> 1842
<212> DNA
<213> Homo sapiens

<220>
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<222> (137)..(1426)

<400> 23
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tcgagactcg cagtcgcggc cactgcagtc acttcgccag ttagccctta gggtaggagt 120

cgcgccggca gcagcc atg agc ggc ggc gtg tac ggg gga gat gaa gtt gga 172
                 Met Ser Gly Gly Val Tyr Gly Gly Asp Glu Val Gly
                   1               5                  10

gcc ctt gtt ttt gac att gga tcc tat act gtg aga gct ggt tat gct  220
Ala Leu Val Phe Asp Ile Gly Ser Tyr Thr Val Arg Ala Gly Tyr Ala
         15                  20                  25

ggt gag gac tgc ccc aag gtg gat ttt cct aca gct att ggt atg gtg  268
Gly Glu Asp Cys Pro Lys Val Asp Phe Pro Thr Ala Ile Gly Met Val
     30                  35                  40

gta gaa aga gat gac gga agc aca tta atg gaa ata gat ggc gat aaa  316
Val Glu Arg Asp Asp Gly Ser Thr Leu Met Glu Ile Asp Gly Asp Lys
 45                  50                  55                  60

ggc aaa caa ggc ggt ccc acc tac tac ata gat act aat gct ctg cgt  364
Gly Lys Gln Gly Gly Pro Thr Tyr Tyr Ile Asp Thr Asn Ala Leu Arg
                 65                  70                  75

gtt ccg agg gag aat atg gag gcc att tca cct cta aaa aat ggg atg  412
Val Pro Arg Glu Asn Met Glu Ala Ile Ser Pro Leu Lys Asn Gly Met
             80                  85                  90

gtt gaa gac tgg gat agt ttc caa gct att ttg gat cat acc tac aaa  460
Val Glu Asp Trp Asp Ser Phe Gln Ala Ile Leu Asp His Thr Tyr Lys
         95                  100                 105

atg cat gtc aaa tca gaa gcc agt ctc cat cct gtt ctc atg tca gag  508
Met His Val Lys Ser Glu Ala Ser Leu His Pro Val Leu Met Ser Glu
    110                 115                 120

gca ccg tgg aat act aga gca aag aga gag aaa ctg aca gag tta atg  556
Ala Pro Trp Asn Thr Arg Ala Lys Arg Glu Lys Leu Thr Glu Leu Met
125                 130                 135                 140

ttt gaa cac tac aac atc cct gcc ttc ttc ctt tgc aaa act gca gtt  604
Phe Glu His Tyr Asn Ile Pro Ala Phe Phe Leu Cys Lys Thr Ala Val
                145                 150                 155

ttg aca gca ttt gct aat ggt cgt tct act ggg ctg att ttg gac agt  652
Leu Thr Ala Phe Ala Asn Gly Arg Ser Thr Gly Leu Ile Leu Asp Ser
            160                 165                 170

gga gcc act cat acc act gca att cca gtc cac gat ggc tat gtc ctt  700
Gly Ala Thr His Thr Thr Ala Ile Pro Val His Asp Gly Tyr Val Leu
        175                 180                 185

caa caa ggc att gtg aaa tcc cct ctt gct gga gac ttt att act atg  748
Gln Gln Gly Ile Val Lys Ser Pro Leu Ala Gly Asp Phe Ile Thr Met
    190                 195                 200
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cag tgc aga gaa ctc ttc caa gaa atg aat att gaa ttg gtt cct cca   796
Gln Cys Arg Glu Leu Phe Gln Glu Met Asn Ile Glu Leu Val Pro Pro
205                 210                 215                 220

tat atg att gca tca aaa gaa gct gtt cgt gaa gga tct cca gca aac   844
Tyr Met Ile Ala Ser Lys Glu Ala Val Arg Glu Gly Ser Pro Ala Asn
                225                 230                 235

tgg aaa aga aaa gag aag ttg cct cag gtt acg agg tct tgg cac aat   892
Trp Lys Arg Lys Glu Lys Leu Pro Gln Val Thr Arg Ser Trp His Asn
            240                 245                 250

tat atg tgt aat tgt gtt atc cag gat ttt caa gct tcg gta ctt caa   940
Tyr Met Cys Asn Cys Val Ile Gln Asp Phe Gln Ala Ser Val Leu Gln
        255                 260                 265

gtg tca gat tca act tat gat gaa caa gtg gct gca cag atg cca act   988
Val Ser Asp Ser Thr Tyr Asp Glu Gln Val Ala Ala Gln Met Pro Thr
    270                 275                 280

gtt cat tat gaa ttc ccc aat ggc tac aat tgt gat ttt ggt gca gag   1036
Val His Tyr Glu Phe Pro Asn Gly Tyr Asn Cys Asp Phe Gly Ala Glu
285                 290                 295                 300

cgg cta aag att cca gaa gga tta ttt gac cct tcc aat gta aag ggg   1084
Arg Leu Lys Ile Pro Glu Gly Leu Phe Asp Pro Ser Asn Val Lys Gly
                305                 310                 315

tta tca gga aac aca atg tta gga gtc agt cat gtt gtc acc aca agt   1132
Leu Ser Gly Asn Thr Met Leu Gly Val Ser His Val Val Thr Thr Ser
            320                 325                 330

gtt ggg atg tgt gat att gat atc aga cca ggt ctc tat ggc agt gta   1180
Val Gly Met Cys Asp Ile Asp Ile Arg Pro Gly Leu Tyr Gly Ser Val
        335                 340                 345

ata gtg gca gga gga aac aca cta ata cag agt ttt act gac agg ttg   1228
Ile Val Ala Gly Gly Asn Thr Leu Ile Gln Ser Phe Thr Asp Arg Leu
    350                 355                 360

aat aga gag ctg tct cag aaa act cct cca agt atg cgg ttg aaa ttg   1276
Asn Arg Glu Leu Ser Gln Lys Thr Pro Pro Ser Met Arg Leu Lys Leu
365                 370                 375                 380

att gca aat aat aca aca gtg gaa cgg agg ttt agc tca tgg att ggc   1324
Ile Ala Asn Asn Thr Thr Val Glu Arg Arg Phe Ser Ser Trp Ile Gly
                385                 390                 395

ggc tcc att cta gcc tct ttg ggt acc ttt caa cag atg tgg att tcc   1372
Gly Ser Ile Leu Ala Ser Leu Gly Thr Phe Gln Gln Met Trp Ile Ser
            400                 405                 410

aag caa gaa tat gaa gaa gga ggg aag cag tgt gta gaa aga aaa tgc   1420
Lys Gln Glu Tyr Glu Glu Gly Gly Lys Gln Cys Val Glu Arg Lys Cys
        415                 420                 425
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cct tga gaaagagttc ccaagcttct accttccttt tgtcacctta cgtttcatag 1476
Pro
430

ctttagtata ctcaggaaaa gaatgaccat cttttgtaga atgtttatac atttatgcat 1536

atttcaattt ccacttaaat ttatttaaag ctttaactgg ctctataaat taagtttgtg 1596

ctttccttga aatgcactta ttcttattac aagcatttta taattttgta taaatgtcta 1656

ttttctctaa atattttgct ttcagtaaaa tgctttccaa ctctgtttag tgtattaatt 1716

accagtggat tggtagaact gcttttattg actagtaaaa gttactgcct agtcttttta 1776

ccttaggctt acagaattaa ataaaaatta gccattccag aaatataaaa aaaaaaaaaa 1836

aaaaaa 1842

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<211> 429
<212> PRT
<213> Homo sapiens

<400> 24
Met Ser Gly Gly Val Tyr Gly Gly Asp Glu Val Gly Ala Leu Val Phe
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Asp Ile Gly Ser Tyr Thr Val Arg Ala Gly Tyr Ala Gly Glu Asp Cys
20 25 30

Pro Lys Val Asp Phe Pro Thr Ala Ile Gly Met Val Val Glu Arg Asp
35 40 45

Asp Gly Ser Thr Leu Met Glu Ile Asp Gly Asp Lys Gly Lys Gln Gly
50 55 60

Gly Pro Thr Tyr Tyr Ile Asp Thr Asn Ala Leu Arg Val Pro Arg Glu
65 70 75 80

Asn Met Glu Ala Ile Ser Pro Leu Lys Asn Gly Met Val Glu Asp Trp
85 90 95

Asp Ser Phe Gln Ala Ile Leu Asp His Thr Tyr Lys Met His Val Lys
100 105 110

Ser Glu Ala Ser Leu His Pro Val Leu Met Ser Glu Ala Pro Trp Asn
115 120 125

Thr Arg Ala Lys Arg Glu Lys Leu Thr Glu Leu Met Phe Glu His Tyr
130 135 140

Asn Ile Pro Ala Phe Phe Leu Cys Lys Thr Ala Val Leu Thr Ala Phe
145 150 155 160

```
Ala Asn Gly Arg Ser Thr Gly Leu Ile Leu Asp Ser Gly Ala Thr His
                165                 170                 175

Thr Thr Ala Ile Pro Val His Asp Gly Tyr Val Leu Gln Gln Gly Ile
            180                 185                 190

Val Lys Ser Pro Leu Ala Gly Asp Phe Ile Thr Met Gln Cys Arg Glu
        195                 200                 205

Leu Phe Gln Glu Met Asn Ile Glu Leu Val Pro Pro Tyr Met Ile Ala
    210                 215                 220

Ser Lys Glu Ala Val Arg Glu Gly Ser Pro Ala Asn Trp Lys Arg Lys
225                 230                 235                 240

Glu Lys Leu Pro Gln Val Thr Arg Ser Trp His Asn Tyr Met Cys Asn
                245                 250                 255

Cys Val Ile Gln Asp Phe Gln Ala Ser Val Leu Gln Val Ser Asp Ser
            260                 265                 270

Thr Tyr Asp Glu Gln Val Ala Ala Gln Met Pro Thr Val His Tyr Glu
        275                 280                 285

Phe Pro Asn Gly Tyr Asn Cys Asp Phe Gly Ala Glu Arg Leu Lys Ile
    290                 295                 300

Pro Glu Gly Leu Phe Asp Pro Ser Asn Val Lys Gly Leu Ser Gly Asn
305                 310                 315                 320

Thr Met Leu Gly Val Ser His Val Val Thr Thr Ser Val Gly Met Cys
                325                 330                 335

Asp Ile Asp Ile Arg Pro Gly Leu Tyr Gly Ser Val Ile Val Ala Gly
            340                 345                 350

Gly Asn Thr Leu Ile Gln Ser Phe Thr Asp Arg Leu Asn Arg Glu Leu
        355                 360                 365

Ser Gln Lys Thr Pro Pro Ser Met Arg Leu Lys Leu Ile Ala Asn Asn
    370                 375                 380

Thr Thr Val Glu Arg Arg Phe Ser Ser Trp Ile Gly Gly Ser Ile Leu
385                 390                 395                 400

Ala Ser Leu Gly Thr Phe Gln Gln Met Trp Ile Ser Lys Gln Glu Tyr
                405                 410                 415

Glu Glu Gly Gly Lys Gln Cys Val Glu Arg Lys Cys Pro
            420                 425
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<210> 25
<211> 4077
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (402)..(1823)

<400> 25
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cccagacatc ttcgggctgc tattggattg actttgaagg ttctgtgtgg gtcgccgtgg 120

ctgcatgttt gaatcaggtg gagaagcact tcaacgctgg acgaagtaaa gattattgtt 180

gttatttttt ttttctctct ctctctctct taagaaagga aaatatccca aggactaatc 240

tgatcgggtc ttccttcatc aggaacgaat gcaggaattt gggaactgag ctgtgcaagt 300

gctgaagaag gagatttgtt tggaggaaac aggaaagaga aagaaaagga aggaaaaaat 360

acataatttc agggacgaga gagagaagaa aaacggggac t atg ggg aga aaa aag 416
Met Gly Arg Lys Lys
1 5

att cag att acg agg att atg gat gaa cgt aac aga cag gtg aca ttt 464
Ile Gln Ile Thr Arg Ile Met Asp Glu Arg Asn Arg Gln Val Thr Phe
10 15 20

aca aag agg aaa ttt ggg ttg atg aag aag gct tat gag ctg agc gtg 512
Thr Lys Arg Lys Phe Gly Leu Met Lys Lys Ala Tyr Glu Leu Ser Val
25 30 35

ctg tgt gac tgt gag att gcg ctg atc atc ttc aac agc acc aac aag 560
Leu Cys Asp Cys Glu Ile Ala Leu Ile Ile Phe Asn Ser Thr Asn Lys
40 45 50

ctg ttc cag tat gcc agc acc gac atg gac aaa gtg ctt ctc aag tac 608
Leu Phe Gln Tyr Ala Ser Thr Asp Met Asp Lys Val Leu Leu Lys Tyr
55 60 65

acg gag tac aac gag ccg cat gag agc cgg aca aac tca gac atc gtg 656
Thr Glu Tyr Asn Glu Pro His Glu Ser Arg Thr Asn Ser Asp Ile Val
70 75 80 85

gag acg ttg aga aag aag ggc ctt aat ggc tgt gac agc cca gac ccc 704
Glu Thr Leu Arg Lys Lys Gly Leu Asn Gly Cys Asp Ser Pro Asp Pro
90 95 100

gat gcg gac gat tcc gta ggt cac agc cct gag tct gag gac aag tac 752
Asp Ala Asp Asp Ser Val Gly His Ser Pro Glu Ser Glu Asp Lys Tyr
105 110 115

agg aaa att aac gaa gat att gat cta atg atc agc agg caa aga ttg 800
Arg Lys Ile Asn Glu Asp Ile Asp Leu Met Ile Ser Arg Gln Arg Leu
120 125 130

tgt gct gtt cca cct ccc aac ttc gag atg cca gtc tcc atc cca gtg 848
Cys Ala Val Pro Pro Pro Asn Phe Glu Met Pro Val Ser Ile Pro Val
135 140 145

```
tcc agc cac aac agt ttg gtg tac agc aac cct gtc agc tca ctg gga   896
Ser Ser His Asn Ser Leu Val Tyr Ser Asn Pro Val Ser Ser Leu Gly
150                 155                 160                 165

aac ccc aac cta ttg cca ctg gct cac cct tct ctg cag agg aat agt   944
Asn Pro Asn Leu Leu Pro Leu Ala His Pro Ser Leu Gln Arg Asn Ser
                170                 175                 180

atg tct cct ggt gta aca cat cga cct cca agt gca ggt aac aca ggt   992
Met Ser Pro Gly Val Thr His Arg Pro Pro Ser Ala Gly Asn Thr Gly
            185                 190                 195

ggt ctg atg ggt gga gac ctc acg tct ggt gca ggc acc agt gca ggg   1040
Gly Leu Met Gly Gly Asp Leu Thr Ser Gly Ala Gly Thr Ser Ala Gly
        200                 205                 210

aac ggg tat ggc aat ccc cga aac tca cca ggt ctg ctg gtc tca cct   1088
Asn Gly Tyr Gly Asn Pro Arg Asn Ser Pro Gly Leu Leu Val Ser Pro
    215                 220                 225

ggt aac ttg aac aag aat atg caa gca aaa tct cct ccc cca atg aat   1136
Gly Asn Leu Asn Lys Asn Met Gln Ala Lys Ser Pro Pro Pro Met Asn
230                 235                 240                 245

tta gga atg aat aac cgt aaa cca gat ctc cga gtt ctt att cca cca   1184
Leu Gly Met Asn Asn Arg Lys Pro Asp Leu Arg Val Leu Ile Pro Pro
                250                 255                 260

ggc agc aag aat acg atg cca tca gtg tct gag gat gtc gac ctg ctt   1232
Gly Ser Lys Asn Thr Met Pro Ser Val Ser Glu Asp Val Asp Leu Leu
            265                 270                 275

ttg aat caa agg ata aat aac tcc cag tcg gct cag tca ttg gct acc   1280
Leu Asn Gln Arg Ile Asn Asn Ser Gln Ser Ala Gln Ser Leu Ala Thr
        280                 285                 290

cca gtg gtt tcc gta gca act cct act tta cca gga caa gga atg gga   1328
Pro Val Val Ser Val Ala Thr Pro Thr Leu Pro Gly Gln Gly Met Gly
    295                 300                 305

gga tat cca tca gcc att tca aca aca tat ggt acc gag tac tct ctg   1376
Gly Tyr Pro Ser Ala Ile Ser Thr Thr Tyr Gly Thr Glu Tyr Ser Leu
310                 315                 320                 325

agt agt gca gac ctg tca tct ctg tct ggg ttt aac acc gcc agc gct   1424
Ser Ser Ala Asp Leu Ser Ser Leu Ser Gly Phe Asn Thr Ala Ser Ala
                330                 335                 340

ctt cac ctt ggt tca gta act ggc tgg caa cag caa cac cta cat aac   1472
Leu His Leu Gly Ser Val Thr Gly Trp Gln Gln Gln His Leu His Asn
            345                 350                 355

atg cca cca tct gcc ctc agt cag ttg gga gct tgc act agc act cat   1520
Met Pro Pro Ser Ala Leu Ser Gln Leu Gly Ala Cys Thr Ser Thr His
        360                 365                 370
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tta tct cag agt tca aat ctc tcc ctg cct tct act caa agc etc aac   1568
Leu Ser Gln Ser Ser Asn Leu Ser Leu Pro Ser Thr Gln Ser Leu Asn
    375                 380                 385

atc aag tca gaa cct gtt tct cct cct aga gac cgt acc acc acc cct   1616
Ile Lys Ser Glu Pro Val Ser Pro Pro Arg Asp Arg Thr Thr Thr Pro
390                 395                 400                 405

tcg aga tac cca caa cac acg cgc cac gag gcg ggg aga tct cct gtt   1664
Ser Arg Tyr Pro Gln His Thr Arg His Glu Ala Gly Arg Ser Pro Val
                410                 415                 420

gac agc ttg agc agc tgt agc agt tcg tac gac ggg agc gac cga gag   1712
Asp Ser Leu Ser Ser Cys Ser Ser Ser Tyr Asp Gly Ser Asp Arg Glu
            425                 430                 435

gat cac cgg aac gaa ttc cac tcc ccc att gga ctc acc aga cct tcg   1760
Asp His Arg Asn Glu Phe His Ser Pro Ile Gly Leu Thr Arg Pro Ser
        440                 445                 450

ccg gac gaa agg gaa agt ccc tca gtc aag cgc atg cga ctt tct gaa   1808
Pro Asp Glu Arg Glu Ser Pro Ser Val Lys Arg Met Arg Leu Ser Glu
    455                 460                 465

gga tgg gca aca tga tcagattatt acttactagt ttttttttt ttcttgcagt   1863
Gly Trp Ala Thr
470

gtgtgtgtgt gctatacctt aatggggaag gggggtcgat atgcattata tgtgccgtgt 1923

gtggaaaaaa aaaaagtcag gtactctgtt ttgtaaaagt acttttaaat tgcctcagtg 1983

atacagtata aagataaaca gaaatgctga gataagctta gcacttgagt tgtacaacag 2043

aacacttgta caaaatagat tttaaggcta acttcttttc actgttgtgc tcctttgcaa 2103

aatgtatgtt acaatagata gtgtcatgtt gcaggttcaa cgttatttac atgtaaatag 2163

acaaaaggaa acatttgcca aaagcggcag atctttactg aaagagagag cagctgttat 2223

gcaacatata gaaaaatgta tagatgcttg gacagacccg gtaatgggtg gccattggta 2283

aatgttagga acacaccagg tcacctgaca tcccaagaat gctcacaaac ctgcaggcat 2343

atcattggcg tatggcactc attaaaaagg atcagagacc attaaaagag gaccatacct 2403

attaaaaaaa aatgtggagt tggagggcta acatatttaa ttaaataaat aaataaatct 2463

gggtctgcat ctcttattaa ataaaaatat aaaaatatgt acattacatt ttgcttattt 2523

tcatataaaa ggtaagacag agtttgcaaa gcatttgtgg ctttttgtag tttacttaag 2583

ccaaaatgtg ttttttttccc cttgatagct tcgctaatat tttaaacagt cctgtaaaaa 2643

accaaaaagg acttttttgta tagaaagcac taccctaagc catgaagaac tccatgcttt 2703
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gctaaccaag ataactgttt tctctttgta gaagttttgt ttttgaaatg tgtatttcta 2763

attatataaa atattaagaa tcttttaaaa aaatctgtga aattaacatg cttgtgtata 2823

gctttctaat atatataata ttatggtaat agcagaagtt ttgttatctt aatagcggga 2883

ggggggtata tttgtgcagt tgcacatttg agtaactatt ttctttctgt tttcttttac 2943

tctgcttaca ttttataagt ttaaggtcag ctgtcaaaag gataacctgt ggggttagaa 3003

catatcacat tgcaacaccc taaattgttt ttaatacatt agcaatctat tgggtcaact 3063

gacatccatt gtatatacta gtttctttca tgctattttt attttgtttt ttgcattttt 3123

atcaaatgca gggccccttt ctgatctcac catttcacca tgcatcttgg aattcagtaa 3183

gtgcatatcc taacttgccc atattctaaa tcatctggtt ggttttcagc ctagaatttg 3243

atacgctttt tagaaatatg cccagaatag aaaagctatg ttggggcaca tgtcctgcaa 3303

atatggccct agaaacaagt gatatggaat ttacttggtg aataagttat aaattcccac 3363

agaagaaaaa tgtgaaagac tgggtgctag acaagaagga agcaggtaaa gggatagttg 3423

ctttgtcatc cgtttttaat tattttaact gacccttgac aatcttgtca gcaatatagg 3483

actgttgaac aatcccggtg tgtcaggacc cccaaatgtc acttctgcat aaagcatgta 3543

tgtcatctat tttttcttca ataaagagat ttaatagcca tttcaagaaa tcccataaag 3603

aacctctcta tgtccctttt tttaatttaa aaaaatgact cttgtctaat attcgtctat 3663

aagggattaa ttttcagacc ctttaataag tgagtgccat aagaaagtca atatatattg 3723

tttaaaagat atttcagtct aggaaagatt ttccttctct tggaatgtga agatctgtcg 3783

attcatctcc aatcatatgc attgacatac acagcaaaga agatataggc agtaatatca 3843

acactgctat atcatgtgta ggacatttct tatccatttt ttctctttta cttgcatagt 3903

tgctatgtgt ttctcattgt aaaaggctgc cgctgggtgg cagaagccaa gagaccttat 3963

taactaggct atatttttct taacttgatc tgaaatccac aattagacca caatgcacct 4023

ttggttgtat ccataaagga tgctagcctg ccttgtacta atgttttata tatt 4077

<210> 26
<211> 473
<212> PRT
<213> Homo sapiens

<400> 26

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Met Gly Arg Lys Lys Ile Gln Ile Thr Arg Ile Met Asp Glu Arg Asn
 1               5                  10                  15

Arg Gln Val Thr Phe Thr Lys Arg Lys Phe Gly Leu Met Lys Lys Ala
            20                  25                  30

Tyr Glu Leu Ser Val Leu Cys Asp Cys Glu Ile Ala Leu Ile Ile Phe
        35                  40                  45

Asn Ser Thr Asn Lys Leu Phe Gln Tyr Ala Ser Thr Asp Met Asp Lys
    50                  55                  60

Val Leu Leu Lys Tyr Thr Glu Tyr Asn Glu Pro His Glu Ser Arg Thr
65                  70                  75                  80

Asn Ser Asp Ile Val Glu Thr Leu Arg Lys Lys Gly Leu Asn Gly Cys
                85                  90                  95

Asp Ser Pro Asp Pro Asp Ala Asp Asp Ser Val Gly His Ser Pro Glu
            100                 105                 110

Ser Glu Asp Lys Tyr Arg Lys Ile Asn Glu Asp Ile Asp Leu Met Ile
        115                 120                 125

Ser Arg Gln Arg Leu Cys Ala Val Pro Pro Pro Asn Phe Glu Met Pro
    130                 135                 140

Val Ser Ile Pro Val Ser Ser His Asn Ser Leu Val Tyr Ser Asn Pro
145                 150                 155                 160

Val Ser Ser Leu Gly Asn Pro Asn Leu Leu Pro Leu Ala His Pro Ser
                165                 170                 175

Leu Gln Arg Asn Ser Met Ser Pro Gly Val Thr His Arg Pro Pro Ser
            180                 185                 190

Ala Gly Asn Thr Gly Gly Leu Met Gly Gly Asp Leu Thr Ser Gly Ala
        195                 200                 205

Gly Thr Ser Ala Gly Asn Gly Tyr Gly Asn Pro Arg Asn Ser Pro Gly
    210                 215                 220

Leu Leu Val Ser Pro Gly Asn Leu Asn Lys Asn Met Gln Ala Lys Ser
225                 230                 235                 240

Pro Pro Pro Met Asn Leu Gly Met Asn Asn Arg Lys Pro Asp Leu Arg
                245                 250                 255

Val Leu Ile Pro Pro Gly Ser Lys Asn Thr Met Pro Ser Val Ser Glu
            260                 265                 270

Asp Val Asp Leu Leu Leu Asn Gln Arg Ile Asn Asn Ser Gln Ser Ala
        275                 280                 285

Gln Ser Leu Ala Thr Pro Val Val Ser Val Ala Thr Pro Thr Leu Pro
    290                 295                 300
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Gly Gln Gly Met Gly Gly Tyr Pro Ser Ala Ile Ser Thr Thr Tyr Gly
305                 310                 315                 320

Thr Glu Tyr Ser Leu Ser Ser Ala Asp Leu Ser Ser Leu Ser Gly Phe
                325                 330                 335

Asn Thr Ala Ser Ala Leu His Leu Gly Ser Val Thr Gly Trp Gln Gln
            340                 345                 350

Gln His Leu His Asn Met Pro Pro Ser Ala Leu Ser Gln Leu Gly Ala
        355                 360                 365

Cys Thr Ser Thr His Leu Ser Gln Ser Ser Asn Leu Ser Leu Pro Ser
    370                 375                 380

Thr Gln Ser Leu Asn Ile Lys Ser Glu Pro Val Ser Pro Pro Arg Asp
385                 390                 395                 400

Arg Thr Thr Thr Pro Ser Arg Tyr Pro Gln His Thr Arg His Glu Ala
                405                 410                 415

Gly Arg Ser Pro Val Asp Ser Leu Ser Ser Cys Ser Ser Ser Tyr Asp
            420                 425                 430

Gly Ser Asp Arg Glu Asp His Arg Asn Glu Phe His Ser Pro Ile Gly
        435                 440                 445

Leu Thr Arg Pro Ser Pro Asp Glu Arg Glu Ser Pro Ser Val Lys Arg
    450                 455                 460

Met Arg Leu Ser Glu Gly Trp Ala Thr
465                 470


<210> 27
<211> 1599
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (86)..(1285)

<400> 27
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gagaccaaga agcgggacgt tcacc atg gga aga aaa tcg ctg tac ctt ctg   112
                           Met Gly Arg Lys Ser Leu Tyr Leu Leu
                             1               5

att gtg ggg atc ctc ata gca tat tat att tat acg cct ctc cca gat   160
Ile Val Gly Ile Leu Ile Ala Tyr Tyr Ile Tyr Thr Pro Leu Pro Asp
 10                  15                  20                  25
```

```
aac gtt gag gag cca tgg aga atg atg tgg ata aac gca cat ctg aaa   208
Asn Val Glu Glu Pro Trp Arg Met Met Trp Ile Asn Ala His Leu Lys
                30                  35                  40

act ata caa aat ttg gct aca ttt gtg gag ctc cat ggg agt tcc att   256
Thr Ile Gln Asn Leu Ala Thr Phe Val Glu Leu His Gly Ser Ser Ile
            45                  50                  55

ttt atg gat tcc ttt aag gtt gtc ggg agc ttt gat gaa gtc cca cca   304
Phe Met Asp Ser Phe Lys Val Val Gly Ser Phe Asp Glu Val Pro Pro
        60                  65                  70

acc tca gat gaa aat gtc act gtg act gag aca aaa ttc aac aac att   352
Thr Ser Asp Glu Asn Val Thr Val Thr Glu Thr Lys Phe Asn Asn Ile
    75                  80                  85

ctt gtt cgg gta tat gtg cca aag aga aag tct gaa gca cta aga agg   400
Leu Val Arg Val Tyr Val Pro Lys Arg Lys Ser Glu Ala Leu Arg Arg
90                  95                  100                 105

ggg ttg ttt tac atc cat ggt gga ggc tgg tgc gtg gga agt gct gct   448
Gly Leu Phe Tyr Ile His Gly Gly Gly Trp Cys Val Gly Ser Ala Ala
                110                 115                 120

cta agt ggt tat gac ttg ctg tca aga tgg aca gca gac aga ctt gat   496
Leu Ser Gly Tyr Asp Leu Leu Ser Arg Trp Thr Ala Asp Arg Leu Asp
            125                 130                 135

gct gtc gtc gta tca acc aac tac aga tta gca cct aag tat cat ttc   544
Ala Val Val Val Ser Thr Asn Tyr Arg Leu Ala Pro Lys Tyr His Phe
        140                 145                 150

cca att caa ttt gaa gat gta tat aat gcc tta agg tgg ttc tta cgt   592
Pro Ile Gln Phe Glu Asp Val Tyr Asn Ala Leu Arg Trp Phe Leu Arg
    155                 160                 165

aaa aaa gtt ctt gca aaa tat ggt gtg aac cct gag aga atc ggt att   640
Lys Lys Val Leu Ala Lys Tyr Gly Val Asn Pro Glu Arg Ile Gly Ile
170                 175                 180                 185

tct gga gat agt gca gga ggg aat tta gct gca gca gtg act caa cag   688
Ser Gly Asp Ser Ala Gly Gly Asn Leu Ala Ala Ala Val Thr Gln Gln
                190                 195                 200

ctc ctt gat gac cca gat gtc aag atc aaa ctc aag atc cag tct tta   736
Leu Leu Asp Asp Pro Asp Val Lys Ile Lys Leu Lys Ile Gln Ser Leu
            205                 210                 215

att tat cct gcc ctt cag cct ctt gat gta gat tta ccg tca tat caa   784
Ile Tyr Pro Ala Leu Gln Pro Leu Asp Val Asp Leu Pro Ser Tyr Gln
        220                 225                 230

gaa aat tca aat ttt cta ttt cta tcc aaa tca ctc atg gtc aga ttc   832
Glu Asn Ser Asn Phe Leu Phe Leu Ser Lys Ser Leu Met Val Arg Phe
    235                 240                 245
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tgg agt gaa tat ttt acc act gat aga tca ctt gaa aaa gcc atg ctt   880
Trp Ser Glu Tyr Phe Thr Thr Asp Arg Ser Leu Glu Lys Ala Met Leu
250                 255                 260                 265

tcc aga caa cat gta cct gtg gaa tca agt cat ctc ttc aaa ttt att   928
Ser Arg Gln His Val Pro Val Glu Ser Ser His Leu Phe Lys Phe Ile
                270                 275                 280

aat tgg agt tcc ctg ctc cct gag agg ttt ata aaa gga cat gtt tat   976
Asn Trp Ser Ser Leu Leu Pro Glu Arg Phe Ile Lys Gly His Val Tyr
            285                 290                 295

aac aat cca aat tat ggc agt tct gag ctg gct aaa aaa tat cca ggg   1024
Asn Asn Pro Asn Tyr Gly Ser Ser Glu Leu Ala Lys Lys Tyr Pro Gly
        300                 305                 310

ttc cta gat gtg agg gca gcc cct ttg ttg gct gat gac aac aaa tta   1072
Phe Leu Asp Val Arg Ala Ala Pro Leu Leu Ala Asp Asp Asn Lys Leu
    315                 320                 325

cgt ggc tta ccc ctg acc tat gtc atc acc tgt caa tat gat ctc tta   1120
Arg Gly Leu Pro Leu Thr Tyr Val Ile Thr Cys Gln Tyr Asp Leu Leu
330                 335                 340                 345

aga gat gat gga ctc atg tat gtc acc cga ctt cgc aac act ggg gtt   1168
Arg Asp Asp Gly Leu Met Tyr Val Thr Arg Leu Arg Asn Thr Gly Val
                350                 355                 360

cag gtg act cat aac cat gtt gag gat gga ttc cat gga gca ttt tca   1216
Gln Val Thr His Asn His Val Glu Asp Gly Phe His Gly Ala Phe Ser
            365                 370                 375

ttt ctg gga ctt aaa att agt cac aga ctt ata aat cag tat att gag   1264
Phe Leu Gly Leu Lys Ile Ser His Arg Leu Ile Asn Gln Tyr Ile Glu
        380                 385                 390

tgg cta aag gaa aat cta tag taaaacatgt agctataaca tattttaaaa      1315
Trp Leu Lys Glu Asn Leu
    395                 400

ataaaatctg aaaacctcag aaaatttcga ttagaaattg gtctttctta gaatggtcta 1375

gttaagttcc acatgtagca taattcttaa ataggcactt ttctgttttt tttttcttac 1435

tgtgggattt catttcaatt ttctacattg tctatctgct ttttcggaga ttttccttct 1495

tacactgtta atcttatttt aaaaaatatt acattcttgt atactttatt tttgtgagtt 1555

ggctactatt tacgatgcaa gagaataaat gtgagcaaag attg                  1599


<210> 28
<211> 399
<212> PRT
<213> Homo sapiens
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<400> 28

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Met Gly Arg Lys Ser Leu Tyr Leu Leu Ile Val Gly Ile Leu Ile Ala
 1               5                  10                  15

Tyr Tyr Ile Tyr Thr Pro Leu Pro Asp Asn Val Glu Glu Pro Trp Arg
            20                  25                  30

Met Met Trp Ile Asn Ala His Leu Lys Thr Ile Gln Asn Leu Ala Thr
        35                  40                  45

Phe Val Glu Leu His Gly Ser Ser Ile Phe Met Asp Ser Phe Lys Val
    50                  55                  60

Val Gly Ser Phe Asp Glu Val Pro Pro Thr Ser Asp Glu Asn Val Thr
65                  70                  75                  80

Val Thr Glu Thr Lys Phe Asn Asn Ile Leu Val Arg Val Tyr Val Pro
                85                  90                  95

Lys Arg Lys Ser Glu Ala Leu Arg Arg Gly Leu Phe Tyr Ile His Gly
            100                 105                 110

Gly Gly Trp Cys Val Gly Ser Ala Ala Leu Ser Gly Tyr Asp Leu Leu
        115                 120                 125

Ser Arg Trp Thr Ala Asp Arg Leu Asp Ala Val Val Val Ser Thr Asn
    130                 135                 140

Tyr Arg Leu Ala Pro Lys Tyr His Phe Pro Ile Gln Phe Glu Asp Val
145                 150                 155                 160

Tyr Asn Ala Leu Arg Trp Phe Leu Arg Lys Lys Val Leu Ala Lys Tyr
                165                 170                 175

Gly Val Asn Pro Glu Arg Ile Gly Ile Ser Gly Asp Ser Ala Gly Gly
            180                 185                 190

Asn Leu Ala Ala Ala Val Thr Gln Gln Leu Leu Asp Asp Pro Asp Val
        195                 200                 205

Lys Ile Lys Leu Lys Ile Gln Ser Leu Ile Tyr Pro Ala Leu Gln Pro
    210                 215                 220

Leu Asp Val Asp Leu Pro Ser Tyr Gln Glu Asn Ser Asn Phe Leu Phe
225                 230                 235                 240

Leu Ser Lys Ser Leu Met Val Arg Phe Trp Ser Glu Tyr Phe Thr Thr
                245                 250                 255

Asp Arg Ser Leu Glu Lys Ala Met Leu Ser Arg Gln His Val Pro Val
            260                 265                 270

Glu Ser Ser His Leu Phe Lys Phe Ile Asn Trp Ser Ser Leu Leu Pro
        275                 280                 285
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Glu Arg Phe Ile Lys Gly His Val Tyr Asn Asn Pro Asn Tyr Gly Ser
    290                 295                 300

Ser Glu Leu Ala Lys Lys Tyr Pro Gly Phe Leu Asp Val Arg Ala Ala
305                 310                 315                 320

Pro Leu Leu Ala Asp Asp Asn Lys Leu Arg Gly Leu Pro Leu Thr Tyr
                325                 330                 335

Val Ile Thr Cys Gln Tyr Asp Leu Leu Arg Asp Asp Gly Leu Met Tyr
            340                 345                 350

Val Thr Arg Leu Arg Asn Thr Gly Val Gln Val Thr His Asn His Val
        355                 360                 365

Glu Asp Gly Phe His Gly Ala Phe Ser Phe Leu Gly Leu Lys Ile Ser
    370                 375                 380

His Arg Leu Ile Asn Gln Tyr Ile Glu Trp Leu Lys Glu Asn Leu
385                 390                 395



<210> 29
<211> 1111
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (57)..(911)

<400> 29
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gac gcc atc aag aag aag atg cag atg ctg aag ctc gac aag gag aac  107
Asp Ala Ile Lys Lys Lys Met Gln Met Leu Lys Leu Asp Lys Glu Asn
              5                  10                  15

gcc ttg gat cga gct gag cag gcg gag gcc gac aag aag gcg gcg gaa  155
Ala Leu Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala Glu
         20                  25                  30

gac agg agc aag cag ctg gaa gat gag ctg gtg tca ctg caa aag aaa  203
Asp Arg Ser Lys Gln Leu Glu Asp Glu Leu Val Ser Leu Gln Lys Lys
     35                  40                  45

ctc aag ggc acc gaa gat gaa ctg gac aaa tac tct gag gct ctc aaa  251
Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu Lys
 50                  55                  60                  65

gat gcc cag gag aag ctg gag ctg gca gag aaa aag gcc acc gat gct  299
Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp Ala
                 70                  75                  80
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```
gaa gcc gac gta gct tct ctg aac aga cgc atc cag ctg gtt gag gaa   347
Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu Glu
             85                  90                  95

gag ttg gat cgt gcc cag gag cgt ctg gca aca gct ttg cag aag ctg   395
Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys Leu
        100                 105                 110

gag gaa gct gag aag gca gca gat gag agt gag aga ggc atg aaa gtc   443
Glu Glu Ala Glu Lys Ala Ala Asp Glu Ser Glu Arg Gly Met Lys Val
    115                 120                 125

att gag agt cga gcc caa aaa gat gaa gaa aaa atg gaa att cag gag   491
Ile Glu Ser Arg Ala Gln Lys Asp Glu Glu Lys Met Glu Ile Gln Glu
130                 135                 140                 145

atc caa ctg aaa gag gcc aag cac att gct gaa gat gcc gac cgc aaa   539
Ile Gln Leu Lys Glu Ala Lys His Ile Ala Glu Asp Ala Asp Arg Lys
                150                 155                 160

tac gaa gag gtg gcc cgt aag ctg gtc atc att gag agc gac ctg gaa   587
Tyr Glu Glu Val Ala Arg Lys Leu Val Ile Ile Glu Ser Asp Leu Glu
            165                 170                 175

cgt gca gag gag cgg gct gag ctc tca gaa ggc aaa tgt gcc gag ctt   635
Arg Ala Glu Glu Arg Ala Glu Leu Ser Glu Gly Lys Cys Ala Glu Leu
        180                 185                 190

gaa gaa gaa ttg aaa act gtg acg aac aac ttg aag tca ctg gag gct   683
Glu Glu Glu Leu Lys Thr Val Thr Asn Asn Leu Lys Ser Leu Glu Ala
    195                 200                 205

cag gct gag aag tac tcg cag aag gaa gac aga tat gag gaa gag atc   731
Gln Ala Glu Lys Tyr Ser Gln Lys Glu Asp Arg Tyr Glu Glu Glu Ile
210                 215                 220                 225

aag gtc ctt tcc gac aag ctg aag gag gct gag act cgg gct gag ttt   779
Lys Val Leu Ser Asp Lys Leu Lys Glu Ala Glu Thr Arg Ala Glu Phe
                230                 235                 240

gcg gag agg tca gta act aaa ttg gag aaa agc att gat gac tta gaa   827
Ala Glu Arg Ser Val Thr Lys Leu Glu Lys Ser Ile Asp Asp Leu Glu
            245                 250                 255

gac gag ctg tac gct cag aaa ctg aag tac aaa gcc atc agc gag gag   875
Asp Glu Leu Tyr Ala Gln Lys Leu Lys Tyr Lys Ala Ile Ser Glu Glu
        260                 265                 270

ctg gac cac gct ctc aac gat atg act tcc ata taa gtttctttgc        921
Leu Asp His Ala Leu Asn Asp Met Thr Ser Ile
    275                 280                 285

ttcacttctc ccaagactcc ctcgtcgagc tggatgtccc acctctctga gctctgcatt 981
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tgtctattct ccagctgacc ctggttctct ctcttagcat cctgccttag agccaggcac 1041

acactgtgct ttctattgta cagaagctct tcgtttcagt gtcaaataaa cactgtgtaa 1101

gctaaaaaaa 1111

<210> 30
<211> 285
<212> PRT
<213> Homo sapiens

<400> 30
Met Asp Ala Ile Lys Lys Lys Met Gln Met Leu Lys Leu Asp Lys Glu
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Glu Val Val Ala Glu Asn Pro Cys Gln Asn His His Cys Lys His Gly
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225                 230                 235                 240

His Pro Ile Asp Gly Tyr Leu Ser His Thr Glu Leu Ala Pro Leu Arg
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Ala Pro Leu Ile Pro Met Glu His Cys Thr Thr Arg Phe Phe Glu Thr
          260                 265                 270

Cys Asp Leu Asp Asn Asp Lys Tyr Ile Ala Leu Asp Glu Trp Ala Gly
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Cys Phe Gly Ile Lys Gln Lys Asp Ile Asp Lys Asp Leu Val Ile
  290                 295                 300
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(19) World Intellectual Property Organization
International Bureau

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16 August 2001 (16.08.2001)

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(10) International Publication Number
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(21) International Application Number: PCT/GB01/00578

(22) International Filing Date: 9 February 2001 (09.02.2001)

(25) Filing Language: English

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0003207.8	11 February 2000 (11.02.2000)	GB
0003208.6	11 February 2000 (11.02.2000)	GB
0003210.2	11 February 2000 (11.02.2000)	GB
0003212.8	11 February 2000 (11.02.2000)	GB
0003213.6	11 February 2000 (11.02.2000)	GB
0003215.1	11 February 2000 (11.02.2000)	GB
0003216.9	11 February 2000 (11.02.2000)	GB
0003219.3	11 February 2000 (11.02.2000)	GB
0003220.1	11 February 2000 (11.02.2000)	GB
0003221.9	11 February 2000 (11.02.2000)	GB
0003222.7	11 February 2000 (11.02.2000)	GB
0003768.9	17 February 2000 (17.02.2000)	GB

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(72) Inventors; and

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(74) Agent: **IRVINE, Claire, Jonquil**; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report: 7 March 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/59155 A3

(54) Title: INTERFERON-ALPHA INDUCED GENES

(57) Abstract: The present disclosure relates to identification of previously known genes as being genes upregulated by interferon-α administration, in particular the human genes corresponding to the cDNA sequence in GenBank designated g4758303, g5453897, g4505186, g2366751, g33917, g4504962, g3978516, g5924396, g4505656, g1504007, g3702446, g4001802, g292289, g4557226, g4507646 and g4507170. Determination of expression products of these genes is proposed as having utility in predicting responsiveness to treatment with interferon-α and other interferons which act at the Type 1 interferon receptor.

INTERNATIONAL SEARCH REPORT

Inte ɔnal Application No
PCT/GB 01/00578

A. CLASSIFICATION OF SUBJECT MATTER
IPC G01N33/68 C12Q1/68 C07K14/47 C12N15/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, EMBL, SEQUENCE SEARCH, CHEM ABS Data, MEDLINE, EMBASE, LIFESCIENCES

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE EMBL [Online] AC: J05016, 23 April 1990 (1990-04-23) "Protein disulfide isomerase-related protein" XP002175105 see sequence abstract	1-7
Y	& HUANG ET AL.: "Human deoxycytidine kinase. Sequence of cDNA clones and analysis of expression in cell lines with and without enzyme activity" J. BIOL. CHEM., vol. 266, no. 8, 1991, page 5353 XP001019195 the whole document, in particular figure --- -/--	1-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 2001	20. 11. 01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bassias, I

10

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte ɔnal Application No
PCT/GB 01/00578

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JOHNSON E ET AL: "AN ISOFORM OF PROTEIN DISULFIDE ISOMERASE ISOLATED FROM CHRONIC MYELOGENOUS LEUKEMIA CELLS ALTERS COMPLEX FORMATION BETWEEN NUCLEAR PROTEINS AND REGULATORY REGIONS OF INTERFERON-INDUCIBLE GENES" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 20, 1992, pages 14412-14417, XP001012806 ISSN: 0021-9258 the whole document, in particular p. 14416, right-handed column, second paragraph. ---	1-7
Y	EP 0 242 329 A (CIBA GEIGY AG) 21 October 1987 (1987-10-21) the whole document, in particular p. 3, third paragraph; Examples 3 and 4 ---	1-7
Y	HORISBERGER M A ET AL: "1FN-ALPHA INDUCED HUMAN 78 KD PROTEIN: PURIFICATION AND HOMOLOGIES WITH THE MOUSE MX PROTEIN, PRODUCTION OF MONOCLONAL ANTIBODIES, ANDPOTENTIATION EFFECT OF IFN-GAMMA" JOURNAL OF INTERFERON RESEARCH, MARY ANN LIEBERT, INC., NEW YORK, NY, US, vol. 7, 1 August 1987 (1987-08-01), pages 331-343, XP002059946 ISSN: 0197-8357 the whole document ---	1-7
Y	US 5 834 235 A (RICH STEVEN A ET AL) 10 November 1998 (1998-11-10) the whole document, in particular column 1, lines 55-67 and column 2, line 59 - column 3, line 39 -----	1-7

10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 01/00578

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-7 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-7 all partially

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:2, or determining the level of the mRNA encoding said protein.

2. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:4, or determining the level of the mRNA encoding said protein.

3. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:6, or determining the level of the mRNA encoding said protein.

4. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:8, or determining the level of the mRNA encoding said protein.

5. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:10, or determining the level of the mRNA encoding said protein.

6. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:12, or determining the level of the mRNA encoding said protein.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:14, or determining the level of the mRNA encoding said protein.

8. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:16, or determining the level of the mRNA encoding said protein.

9. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:18, or determining the level of the mRNA encoding said protein.

10. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:20, or determining the level of the mRNA encoding said protein.

11. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:22, or determining the level of the mRNA encoding said protein.

12. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:24, or determining the level of the mRNA encoding said protein.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

13. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:26, or determining the level of the mRNA encoding said protein.

14. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:28, or determining the level of the mRNA encoding said protein.

15. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:30, or determining the level of the mRNA encoding said protein.

16. Claims: 1-7 (all partially)

A method of predicting responsiveness of a patient to treatment with a Type I interferon, which comprises determining the level of a protein defined by the sequence set forth in SEQ ID NO NO:32, or determining the level of the mRNA encoding said protein.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ›nal Application No
PCT/GB 01/00578

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0242329 A	21-10-1987	AT 125304 T	15-08-1995
		AU 608216 B2	28-03-1991
		AU 7151087 A	22-10-1987
		CA 1340289 A1	29-12-1998
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		DE 3751409 T2	25-01-1996
		DK 193187 A	16-10-1987
		EP 0242329 A2	21-10-1987
		ES 2074420 T3	16-09-1995
		IE 67564 B1	17-04-1996
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		JP 7236497 A	12-09-1995
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		PT 84670 A ,B	01-05-1987
		US 5466585 A	14-11-1995
		US 5739290 A	14-04-1998
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US 5834235 A	10-11-1998	US 6060279 A	09-05-2000